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FILE COVERS 1907 - 14 Jun 2006 VOL 144 ISS 25  
FILE LAST UPDATED: 13 Jun 2006 (20060613/ED)

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L61 ANSWER 1 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
AN 2005:1240947 HCAPLUS  
DN 144:11582  
ED Entered STN: 24 Nov 2005  
TI Process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt  
IN Wizel, Shlomit; Frenkel, Gustavo; Gome, Boaz  
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.  
SO PCT Int. Appl., 25 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
IC ICM C07C0231-24  
ICS C07C0233-63; A61K0031-16; A61P0003-00  
CC 63-6 (Pharmaceuticals)  
Section cross-reference(s): 34, 75

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005110972	A1	20051124	WO 2005-US16343	20050509
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

US 2006004102	A1	20060105	US 2005-126050	20050509
EP 1656339	A1	20060517	EP 2005-748381	20050509
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU				
PRAI US 2004-569047P	P	20040507		
WO 2005-US16343	W	20050509		

## CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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WO 2005110972	ICM	C07C0231-24
	ICS	C07C0233-63; A61K0031-16; A61P0003-00
	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	ECLA	C07C231/24; C07C233/63
US 2006004102	IPCI	A61K0031-198 [I,A]; A61K0031-185 [I,C*]
	NCL	514/563.000
EP 1656339	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	ECLA	C07C231/24; C07C233/63

AB Anti-hyperglycemic polymorphic **crystalline** forms of **nateglinide** ammonium salt are prepared

ST **nateglinide** ammonium salt polymorphic **cryst** form

IT Bicarbonates  
Carbonates, reactions  
RL: RGT (Reagent); RACT (Reactant or reagent)  
(Group IA and IIA metal, bases; process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Alkali metal hydroxides  
RL: RGT (Reagent); RACT (Reactant or reagent)  
(base; process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Alkali metal hydrides  
Alkaline earth hydroxides  
RL: RGT (Reagent); RACT (Reactant or reagent)  
(bases; process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Crystallization  
Neutralization  
(in a process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Bases, reactions  
RL: RGT (Reagent); RACT (Reactant or reagent)  
(in a process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Diabetes mellitus  
(non-insulin-dependent; process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt for the treatment of)

IT Polymorphism (crystal)  
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt)

IT Hyperglycemia  
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt for the treatment of)

IT Antidiabetic agents  
(process for the preparation of polymorphic **crystalline** forms of **nateglinide** ammonium salt for use as)

IT Drug delivery systems  
 (process for the preparation of polymorphic **crystalline** forms of  
**nateglinide** ammonium salt for use in)

IT 1344-28-1D, Alumina, basic  
 RL: RGT (Reagent); RACT (Reactant or reagent)  
 (base; process for the preparation of polymorphic **crystalline** forms of  
**nateglinide** ammonium salt)

IT 67-56-1, Methanol, uses 7732-18-5, Water, uses  
 RL: NUU (Other use, unclassified); USES (Uses)  
 (process for the preparation of polymorphic **crystalline** forms of  
**nateglinide** ammonium salt)

IT 594837-89-5P  
 RL: PRP (Properties); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation);  
 USES (Uses)  
 (process for the preparation of polymorphic **crystalline** forms of  
**nateglinide** ammonium salt)

IT 1336-21-6, Ammonium hydroxide 7664-41-7, Ammonia, reactions  
 105816-04-4, **Nateglinide**  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (process for the preparation of polymorphic **crystalline** forms of  
**nateglinide** ammonium salt)

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD

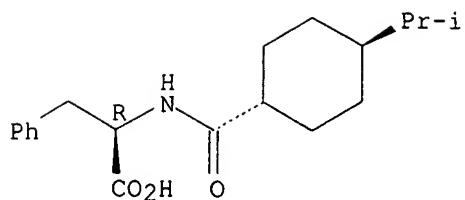
RE

(1) Ajinomoto Co Inc; EP 1334963 A 2003 HCAPLUS  
 (2) Ajinomoto Co Inc; EP 1334964 A 2003 HCAPLUS  
 (3) Ajinomoto Co Inc; EP 1496048 A 2005 HCAPLUS  
 (4) Fre; WO 2004067496 A 2004 HCAPLUS  
 (5) Koguchi, Y; US 5463116 A 1995 HCAPLUS  
 (6) Koguchi, Y; WO 03087039 A1 2003 HCAPLUS  
 (7) Kumashiro, I; US 4816484 A 1989 HCAPLUS  
 (8) LI, G; YAOWU FENXI ZAZHI 2001, V21(5), P342 HCAPLUS  
 (9) Shah, V; WO 03022251 A 2003 HCAPLUS  
 (10) Sutton, P; WO 03076393 A 2003 HCAPLUS  
 (11) Threlfall; ANALYST 1995, V120, P2435 HCAPLUS  
 (12) Yaha; WO 2004009532 A 2004 HCAPLUS

IT 594837-89-5P  
 RL: PRP (Properties); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation);  
 USES (Uses)  
 (process for the preparation of polymorphic **crystalline** forms of  
**nateglinide** ammonium salt)

RN 594837-89-5 HCAPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl)carbonyl]-,  
 ammonium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● x NH<sub>3</sub>

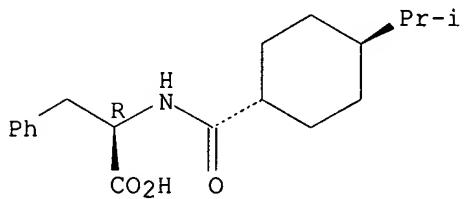
IT 105816-04-4, Nateglinide

RL: RCT (Reactant); RACT (Reactant or reagent)  
(process for the preparation of polymorphic crystalline forms of nateglinide ammonium salt)

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl)carbonyl]- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 2 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN

AN 2005:59980 HCPLUS

DN 142:141289

ED Entered STN: 21 Jan 2005

TI Crystalline form of nateglinide

IN Frenkel, Gustavo; Gome, Boaz; Wizel, Shlomit

PA Israel

SO U.S. Pat. Appl. Publ., 91 pp., Cont.-in-part of U.S. Ser. No. 622,905.

CODEN: USXXCO

DT Patent

LA English

IC ICM A61K0031-198

ICS C07C0233-29

INCL 514563000; 562450000

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 34, 75

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2005014836	A1	20050120	US 2003-746697	20031224 <--
	US 2004181089	A1	20040916	US 2003-622905	20030718 <--
	CA 2513753	AA	20040812	CA 2004-2513753	20040113 <--
	WO 2004067496	A1	20040812	WO 2004-US839	20040113 <--
	WO 2004067496	C2	20041209		

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 GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
 LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI  
 EP 1511717 A1 20050309 EP 2004-701826 20040113 <--  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK  
 PRAI US 2003-442109P P 20030123  
 US 2003-449791P P 20030224  
 US 2003-479016P P 20030616  
 US 2003-622905 A2 20030718 <--  
 US 2002-396904P P 20020718 <--  
 US 2002-413622P P 20020925 <--  
 US 2002-414199P P 20020926 <--  
 US 2002-423750P P 20021105 <--  
 US 2002-432093P P 20021210 <--  
 US 2002-432962P P 20021212 <--  
 WO 2003-US22375 A 20030718  
 US 2003-693166 A 20031023  
 US 2003-746697 A 20031224  
 WO 2004-US839 W 20040113 <--  
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 PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES

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US 2005014836	ICM	A61K0031-198
	ICS	C07C0233-29
	INCL	514563000; 562450000
	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; C07C0233-29 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*]; C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	NCL	514/563.000
	ECLA	A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02; C07C231/24; C07C233/63
US 2004181089	IPCI	C07C0233-30 [ICM,7]; C07C0233-00 [ICM,7,C*]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0051-58 [I,C*]; C07C0051-60 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	NCL	562/450.000
	ECLA	A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02; C07C231/24; C07C233/63
CA 2513753	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; A61P0003-00 [ICS,7]; A61K0031-16 [ICS,7]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61P0003-00 [I,A]; A61P0003-00 [I,C*]; C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
WO 2004067496	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	IPCR	C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	ECLA	C07C231/24; C07C233/63
EP 1511717	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*];

A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]  
 IPCR C07C0231-00 [I,C\*]; C07C0231-24 [I,A]; C07C0233-00  
 [I,C\*]; C07C0233-63 [I,A]

AB Crystalline forms of nateglinide and processes for their preparation, as well as pharmaceutical formulations containing them and methods of administration are provided. A process for preparing crystalline form of nateglinide comprises the steps of (a) preparing a solution of nateglinide in Et acetate, (b) seeding the solution with nateglinide crystals, and (c) recovering the crystalline form as a precipitate. The nateglinide obtained is more than about 99% pure. For example, nateglinide (5 g) was dissolved in acetonitrile, acetone, or Et acetate at about 55° in over about 15 min until a clear solution was obtained. The solvent was removed to dryness by evaporation at about 55°/20 to 30 mmHg to give dry nateglinide crystalline Form B. Also, nateglinide Form Z was prepared by treating 7.73 g of D-phenylalanine (PheOH) with 185 mL (3.5 equiv) of 3.5% NaOH at room temperature to afford a clear solution of

the corresponding Na-salt. A solution of neat trans-4-isopropylcyclohexanecarboxyl chloride (IPCHAC, 9.02 g, 1.01 equiv) was added to the solution of Phe-OH obtained above, over 3 min, while stirring at room temperature. The rest of the IPCHAC in the funnel was washed with toluene (1 mL) and added. The resulting mixture was stirred for 1 h, and was treated with 10% HCl (32 mL) to adjust the pH to 3, while stirring. The mixture was stirred for 1 h, and filtered. The solid was washed with water (200 mL) and sucked well to afford 33.3 g of the moist product, which lost weight after drying at 78°/2.2 mbar (Assay 98.4%, purity >99%, yield 86%).

ST nateglinide crystal form prep polymorphism dosage form

IT Hydrocarbons, processes

RL: PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)

(C5-12; preparation of crystalline form of nateglinide for dosage forms)

IT Solvents

(antisolvents; preparation of crystalline form of nateglinide for dosage forms)

IT Crystal morphology

Crystallization

Drug delivery systems

Polymorphism (crystal)

Precipitation (chemical)

Pulverization

Solvents

(preparation of crystalline form of nateglinide for dosage forms)

IT 105816-04-4P, Nateglinide

RL: PEP (Physical, engineering or chemical process); PRP

(Properties); PYP (Physical process); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study);

PREP (Preparation); PROC (Process); USES (Uses)

(preparation of crystalline form of nateglinide for dosage forms)

IT 56-23-5, Carbontetrachloride, processes 64-17-5, Ethanol, processes 64-19-7, Acetic acid, processes 67-56-1, Methanol, processes 67-63-0, Isopropanol, processes 67-64-1, Acetone, processes 67-66-3, Chloroform, processes 68-12-2, N,N-Dimethylformamide, processes 71-23-8, n-Propanol, processes 71-36-3, n-Butanol, processes 75-05-8,

Acetonitrile, processes 75-09-2, Dichloromethane, processes 75-52-5,  
 Nitromethane, processes 78-93-3, MEK, processes 107-06-2,  
 1,2-Dichloroethane, processes 108-10-1, Methyl isobutyl ketone  
 108-88-3, Toluene, processes 109-99-9, Tetrahydrofuran, processes  
 110-54-3, Hexane, processes 110-71-4 123-91-1, Dioxane, processes  
 127-19-5, N,N-Dimethylacetamide 141-78-6, Ethyl acetate, processes  
 142-82-5, Heptane, processes 563-80-4, Methyl isopropyl ketone  
 872-50-4, N-Methylpyrrolidone, processes 1330-20-7, Xylene, processes  
 RL: PEP (Physical, engineering or chemical process); PYP (Physical  
 process); PROC (Process)

(preparation of **crystalline** form of **nateglinide** for dosage  
 forms)

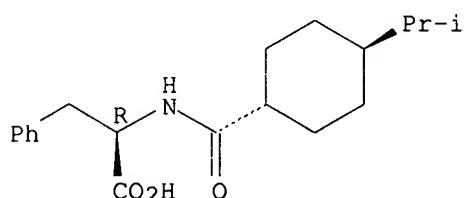
IT 673-06-3, D-Phenylalanine 84855-54-9  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (preparation of **crystalline** form of **nateglinide** for dosage  
 forms)

IT 105816-04-4P, Nateglinide  
 RL: PEP (Physical, engineering or chemical process); PRP  
 (Properties); PYP (Physical process); SPN (Synthetic  
 preparation); THU (Therapeutic use); BIOL (Biological study);  
 PREP (Preparation); PROC (Process); USES (Uses)  
 (preparation of **crystalline** form of **nateglinide** for dosage  
 forms)

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 3 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 2004:648496 HCPLUS

DN 141:179640

ED Entered STN: 12 Aug 2004

TI Preparation of a polymorphic **crystalline** form of the  
 antidiabetic agent **nateglinide**

IN Frenkel, Gustavo; Gome, Boaz; Wizel, Shlomit

PA Teva Pharmaceutical Industries Ltd., Israel; Teva  
 Pharmaceuticals USA, Inc.

SO PCT Int. Appl., 124 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07C0231-24

ICS C07C0233-63; A61K0031-16; A61P0003-00

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 34, 75

FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 2004067496	A1	20040812	WO 2004-US839	20040113 <--

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	WO 2003-US22375	A2	20030718	
	US 2003-693166	A2	20031023	
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## CLASS

	PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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	IPCI	C07C0231-24 [ICM, 7]; C07C0231-00 [ICM, 7, C*]; C07C0233-63 [ICS, 7]; C07C0233-00 [ICS, 7, C*]; A61K0031-16 [ICS, 7]; A61P0003-00 [ICS, 7]	
	IPCR	C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]	
	ECLA	C07C231/24; C07C233/63	
WO 2004009532	IPCI	C07C0231-24 [ICM, 7]; C07C0231-00 [ICM, 7, C*]; C07C0233-63 [ICS, 7]; C07C0233-00 [ICS, 7, C*]; A61K0031-16 [ICS, 7]; A61P0003-00 [ICS, 7]	
	ECLA	A61K031/16; A61K031/198; C07C231/02; C07C231/24; C07C233/63	
US 2004181089	IPCI	C07C0233-30 [ICM, 7]; C07C0233-00 [ICM, 7, C*]	
	IPCR	A61K0031-16 [I, A]; A61K0031-16 [I, C*]; A61K0031-185 [I, C*]; A61K0031-198 [I, A]; C07C0051-58 [I, C*]; C07C0051-60 [I, A]; C07C0231-00 [I, C*]; C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]	

	NCL	562/450.000
	ECLA	A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02; C07C231/24; C07C233/63
US 2005090552	IPCI	C07C0233-87 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; A61K0031-198 [ICS, 7]; A61K0031-185 [ICS, 7, C*]
	IPCR	A61K0031-16 [I, A]; A61K0031-16 [I, C*]; A61K0031-185 [I, C*]; A61K0031-198 [I, A]; C07C0051-58 [I, C*]; C07C0051-60 [I, A]; C07C0231-00 [I, C*]; C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
	NCL	514/563.000
	ECLA	A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02; C07C231/24; C07C233/63
US 2005014836	IPCI	A61K0031-198 [ICM, 7]; A61K0031-185 [ICM, 7, C*]; C07C0233-29 [ICS, 7]; C07C0233-00 [ICS, 7, C*]
	IPCR	A61K0031-16 [I, A]; A61K0031-16 [I, C*]; A61K0031-185 [I, C*]; A61K0031-198 [I, A]; C07C0051-58 [I, C*]; C07C0051-60 [I, A]; C07C0231-00 [I, C*]; C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
	NCL	514/563.000
	ECLA	A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02; C07C231/24; C07C233/63
CA 2513753	IPCI	C07C0231-24 [ICM, 7]; C07C0231-00 [ICM, 7, C*]; A61P0003-00 [ICS, 7]; A61K0031-16 [ICS, 7]; C07C0233-63 [ICS, 7]; C07C0233-00 [ICS, 7, C*]
	IPCR	A61K0031-16 [I, A]; A61K0031-16 [I, C*]; A61P0003-00 [I, A]; A61P0003-00 [I, C*]; C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
EP 1511717	IPCI	C07C0231-24 [ICM, 7]; C07C0231-00 [ICM, 7, C*]; C07C0233-63 [ICS, 7]; C07C0233-00 [ICS, 7, C*]; A61K0031-16 [ICS, 7]; A61P0003-00 [ICS, 7]
	IPCR	C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]

AB The preparation of a polymorphic **crystalline** form (e.g., **form U**) of the antidiabetic agent **nateglinide** is described.

ST **nateglinide** **crystal** polymorphism antidiabetic

IT Hydrocarbons, uses  
RL: NUU (Other use, unclassified); USES (Uses)  
(C5-12, solvents; in the preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide**)

IT Crystallization  
Precipitation (chemical)  
(in the preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide**)

IT Antidiabetic agents  
**Polymorphism (crystal)**  
(preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide**)

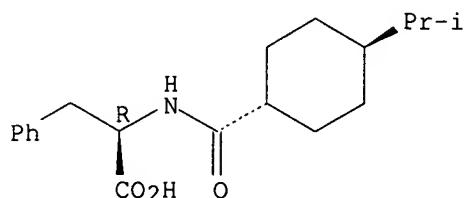
IT Diabetes mellitus  
(preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide** for the treatment of)

IT Drug delivery systems  
(preparation of a polymorphic **crystalline** form of the antidiabetic agent **nateglinide** for use in)

IT 141-78-6, Ethyl acetate, uses 142-82-5, Heptane, uses 7732-18-5, Water, uses  
RL: NUU (Other use, unclassified); USES (Uses)  
(in the preparation of a polymorphic **crystalline** form of the

IT antidiabetic agent nateglinide)  
 IT 105816-04-4, Nateglinide  
 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (preparation of a polymorphic **crystalline** form of the antidiabetic agent nateglinide)  
 IT 105816-04-4, Nateglinide  
 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (preparation of a polymorphic **crystalline** form of the antidiabetic agent nateglinide)  
 RN 105816-04-4 HCPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl)carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 4 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 2004:203799 HCPLUS  
 DN 140:241062  
 ED Entered STN: 14 Mar 2004  
 TI Process for the formation of a **crystalline** polymorphic form of nateglinide  
 IN Reguri, Buchi Reddy; Kadaboina, Rajasekhar; Polavarapu, Srinivas  
 PA Reddy's Laboratories Limited, India; Reddy's Laboratories, Inc.  
 SO PCT Int. Appl., 29 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM C07C0233-63  
 ICS C07C0231-24  
 CC 63-6 (Pharmaceuticals)  
 Section cross-reference(s): 34, 75

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004020396	A1	20040311	WO 2003-US26880	20030827 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003262928	A1	20040319	AU 2003-262928	20030827 <--
	US 2004077725	A1	20040422	US 2003-649380	20030827 <--
PRAI	IN 2002-MA631	A	20020828 <--		

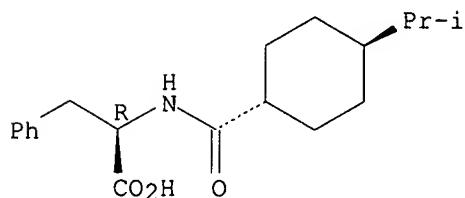
WO 2003-US26880	W 20030827	
CLASS		
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004020396	ICM	C07C0233-63
	ICS	C07C0231-24
	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0231-24 [ICS, 7]; C07C0231-00 [ICS, 7, C*]
	IPCR	A61K0031-185 [I, C*]; A61K0031-198 [I, A]; C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
AU 2003262928	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0231-24 [ICS, 7]; C07C0231-00 [ICS, 7, C*]
	IPCR	A61K0031-185 [I, C*]; A61K0031-198 [I, A]; C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
US 2004077725	IPCI	A61K0031-198 [ICM, 7]; A61K0031-185 [ICM, 7, C*]
	IPCR	A61K0031-185 [I, C*]; A61K0031-198 [I, A]; C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
	NCL	514/563.000
AB	A <b>crystalline polymorphic form</b> of nateglinide are described and its X-ray diffraction pattern presented.	
ST	<b>crystal polymorphism nateglinide</b>	
IT	<b>Crystallization</b> (in a process for the formation of a <b>crystalline polymorphic form</b> of nateglinide)	
IT	Drug delivery systems (oral; process for the formation of a <b>crystalline polymorphic form</b> of nateglinide)	
IT	<b>Polymorphism (crystal)</b> (process for the formation of a <b>crystalline polymorphic form</b> of nateglinide)	
IT	Aromatic hydrocarbons, uses RL: NUU (Other use, unclassified); USES (Uses) (solvents; in a process for the formation of a <b>crystalline polymorphic form</b> of nateglinide)	
IT	Drug delivery systems (tablets; process for the formation of a <b>crystalline polymorphic form</b> of nateglinide)	
IT	95-47-6, o-Xylene, uses RL: NUU (Other use, unclassified); USES (Uses) (process for the formation of a <b>crystalline polymorphic form</b> of nateglinide)	
IT	105816-04-4P, Nateglinide RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses) (process for the formation of a <b>crystalline polymorphic form</b> of nateglinide)	
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD		
RE	(1) Alembic Ltd; WO 03022251 A 2003 HCPLUS (2) Biocon India Ltd; WO 03093222 A 2003 HCPLUS (3) Koguchi, Y; US 5463116 A 1995 HCPLUS (4) Koguchi, Y; WO 03087039 A 2003 HCPLUS (5) LI, G; CHINESE CHEMICAL LETTERS 2003, V14(7), P730 HCPLUS (6) LI, G; YAOWU FENXI ZAZHI 2001, V21(5), P342 HCPLUS (7) Novartis Pharma Gmbh; WO 03087038 A 2003 HCPLUS	
IT	105816-04-4P, Nateglinide	

RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses) (process for the formation of a crystalline polymorphic form of nateglinide)

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 5 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN

AN 2004:80637 HCPLUS

DN 140:151932

ED Entered STN: 01 Feb 2004

TI Preparation of polymorphic forms of nateglinide

IN Yahalom, Ronit; Shapir, Evgeny; Dolitzky, Ben-zion; Gozlan, Yigael; Gome, Boaz

PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceutical USA, Inc.

SO PCT Int. Appl., 130 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07C0231-24

ICS C07C0233-63; A61K0031-16; A61P0003-00

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 75

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004009532	A1	20040129	WO 2003-US22375	20030718 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004152782	A1	20040805	US 2003-614266	20030703 <--
	US 6861553	B2	20050301		
	CA 2492644	AA	20040129	CA 2003-2492644	20030718 <--
	AU 2003253971	A1	20040209	AU 2003-253971	20030718 <--
	US 2004116526	A1	20040617	US 2003-623237	20030718 <--
	EP 1467964	A1	20041020	EP 2003-765665	20030718 <--
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US 2005075400	A1	20050407	US 2003-622999	20030718 <--
CN 1723190	A	20060118	CN 2003-821921	20030718 <--
JP 2006511614	T2	20060406	JP 2005-505521	20030718 <--
CA 2513753	AA	20040812	CA 2004-2513753	20040113 <--
WO 2004067496	A1	20040812	WO 2004-US839	20040113 <--
WO 2004067496	C2	20041209		
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EP 1511717	A1	20050309	EP 2004-701826	20040113 <--
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US 2002-413622P	P	20020925	<--	
US 2002-414199P	P	20020926	<--	
US 2002-423750P	P	20021105	<--	
US 2002-432093P	P	20021210	<--	
US 2002-432962P	P	20021212	<--	
US 2003-442109P	P	20030123		
US 2003-449791P	P	20030224		
US 2003-479016P	P	20030616		
US 2003-614266	A	20030703		
US 2002-393495P	P	20020703	<--	
US 2003-622905	A	20030718	<--	
WO 2003-US22375	W	20030718		
US 2003-693166	A	20031023		
US 2003-746697	A	20031224		
WO 2004-US839	W	20040113	<--	

## CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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WO 2004009532	ICM	C07C0231-24
	ICS	C07C0233-63; A61K0031-16; A61P0003-00
	IPCI	C07C0231-24 [ICM, 7]; C07C0231-00 [ICM, 7, C*]; C07C0233-63 [ICS, 7]; C07C0233-00 [ICS, 7, C*]; A61K0031-16 [ICS, 7]; A61P0003-00 [ICS, 7]
	IPCR	A61K0031-16 [I, A]; A61K0031-16 [I, C*]; A61K0031-185 [I, C*]; A61K0031-198 [I, A]; C07C0231-00 [I, C*]; C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
	ECLA	A61K031/16; A61K031/198; C07C231/02; C07C231/24; C07C233/63
US 2004152782	IPCI	A61K0031-198 [ICM, 7]; A61K0031-185 [ICM, 7, C*]; C07C0231-02 [ICS, 7]; C07C0231-00 [ICS, 7, C*]
	IPCR	A61K0031-16 [I, A]; A61K0031-16 [I, C*]; A61K0031-185 [I, C*]; A61K0031-198 [I, A]; C07C0051-58 [I, C*]; C07C0051-60 [I, A]; C07C0231-00 [I, C*]; C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
	NCL	514/563.000
	ECLA	A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02; C07C231/24; C07C233/63
CA 2492644	IPCI	C07C0231-24 [ICM, 7]; C07C0231-00 [ICM, 7, C*]; A61P0003-00 [ICS, 7]; A61K0031-16 [ICS, 7]; C07C0233-63 [ICS, 7]; C07C0233-00 [ICS, 7, C*]
	IPCR	A61K0031-16 [I, A]; A61K0031-16 [I, C*]; A61K0031-185 [I, C*]; A61K0031-198 [I, A]; C07C0231-00 [I, C*]; C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0233-00

AU 2003253971	IPCI	[I,C*]; C07C0233-63 [I,A] C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
US 2004116526	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0231-00 [I,C*]; C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C*]; C07C0233-63 [N,A]
	NCL	514/563.000
EP 1467964	ECLA	A61K031/16; A61K031/198; C07C231/02; C07C231/24
	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
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US 2005014949	IPCI	C07D0417-04 [ICM,7]; C07D0417-00 [ICM,7,C*]
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	NCL	546/270.400
	ECLA	A61K031/198
US 2005075400	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; C07C0233-61 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	NCL	514/563.000
	ECLA	C07C231/24; C07C233/63
CN 1723190	IPCI	C07C0231-24 [I,A]; C07C0231-00 [I,C*]; C07C0233-63 [I,A]; C07C0233-00 [I,C*]; A61K0031-16 [I,A]; A61P0003-00 [I,A]
JP 2006511614	IPCI	C07C0231-24 [I,A]; C07C0231-00 [I,C*]; A61K0031-198 [I,A]; A61K0031-185 [I,C*]; A61P0003-10 [I,A]; A61P0003-00 [I,C*]; C07C0233-63 [I,A]; C07C0233-00 [I,C*]
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CA 2513753	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; A61P0003-00 [ICS,7]; A61K0031-16 [ICS,7]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]
	IPCR	A61K0031-16 [I,A]; A61K0031-16 [I,C*]; A61P0003-00 [I,A]; A61P0003-00 [I,C*]; C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
WO 2004067496	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*]; A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]
	IPCR	C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	ECLA	C07C231/24; C07C233/63
EP 1511717	IPCI	C07C0231-24 [ICM,7]; C07C0231-00 [ICM,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00 [ICS,7,C*];

A61K0031-16 [ICS,7]; A61P0003-00 [ICS,7]  
 IPCR C07C0231-00 [I,C\*]; C07C0231-24 [I,A]; C07C0233-00  
 [I,C\*]; C07C0233-63 [I,A]

AB The invention discloses the preparation of 26 characterized forms of **nateglinide** (forms A, C, D, F, G, I, J, K, L, M, N, O, P, Q, T, U, V, Y,  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ ,  $\sigma$ ,  $\theta$  and  $\Omega$ ). Most of the forms are solvates (with the exception of forms L, P, U,  $\alpha$ ,  $\delta$  and  $\sigma$ ). Polymorphic forms are characterized by their mp, DSC, XRPD, FTIR; form interconversion is also discussed. For example, D-phenylalanine is reacted with trans-[(4-(isopropyl)cyclohexanee)carbonyl]chloride (i. NaOHaq; ii. H2SO4). The wet cake of **nateglinide** is dissolved in EtOAc, the aqueous phase is removed and the resulting solution heated to 50° under reduced pressure and added to hot heptane. The resulting solution is cooled and seeded with the B-form to afford the  $\delta$ -form (33% yield).

ST polymorphic **nateglinide** blood sugar lowering prepn

IT Fluidized beds  
 (dryers; preparation of polymorphic forms of **nateglinide**)

IT Drying apparatus  
 (fluidized-bed; preparation of polymorphic forms of **nateglinide**)

IT Solvents  
 (**nateglinide** solvate; preparation of polymorphic forms of **nateglinide**)

IT Crystal nucleation  
 Crystallization  
 Human  
 Polymorphism (crystal)  
 Slurries  
 (preparation of polymorphic forms of **nateglinide**)

IT 50-99-7, D-Glucose, biological studies  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (blood, lowering, treatment; preparation of polymorphic forms of **nateglinide**)

IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0, Isopropanol, uses 67-64-1, Acetone, uses 71-23-8, n-Propanol, uses 71-36-3, n-Butanol, uses 75-05-8, Acetonitrile, uses 75-52-5, Nitromethane, uses 78-93-3, Methyl ethyl ketone, uses 108-10-1, Methyl isobutyl ketone 108-88-3, Toluene, uses 110-54-3, Hexane, uses 141-78-6, Ethyl acetate, uses 142-82-5, Heptane, uses 563-80-4, Methyl isopropyl ketone 1330-20-7, Xylene, uses  
 RL: NUU (Other use, unclassified); USES (Uses)  
 (**nateglinide** solvate; preparation of polymorphic forms of **nateglinide**)

IT 67-66-3, Chloroform, uses 109-99-9, Tetrahydrofuran, uses 123-91-1, Dioxane, uses  
 RL: NUU (Other use, unclassified); USES (Uses)  
 (preparation of polymorphic forms of **nateglinide**)

IT 105816-04-4P, **Nateglinide**  
 RL: PEP (Physical, engineering or chemical process); PYP (Physical process); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)  
 (preparation of polymorphic forms of **nateglinide**)

IT 105816-04-4DP, **Nateglinide**, polymorphs 651353-42-3P  
 651353-43-4P 651353-44-5P 651353-45-6P 651353-46-7P 651353-47-8P  
 651353-48-9P 651353-49-0P 651353-50-3P 651353-51-4P 651353-52-5P  
 651353-53-6P 651353-54-7P  
 RL: PEP (Physical, engineering or chemical process); PYP (Physical process); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation);  
 PROC (Process); USES (Uses)

(preparation of polymorphic forms of nateglinide)

IT 673-06-3, D-Phenylalanine 84855-54-9, trans-[(4-  
 (Isopropyl)cyclohexane]carbonyl]chloride

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of polymorphic forms of nateglinide)

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Ajinomoto Co Inc; EP 1334963 A 2003 HCPLUS

(2) Ajinomoto Co Inc; EP 1334964 A 2003 HCPLUS

(3) Alembic Ltd; WO 03022251 A 2003 HCPLUS

(4) Koguchi, Y; US 5463116 A 1995 HCPLUS

(5) Koguchi, Y; WO 2003087039 2003 HCPLUS

(6) Kumashiro, I; US 4816484 A 1989 HCPLUS

(7) LI, G; YAOWU FENXI ZAZHI 2001, V21(5), P342 HCPLUS

(8) Sumikawa, M; WO 2002034713 A 2002 HCPLUS

(9) Takahashi, D; WO 2002032854 A 2002 HCPLUS

IT 105816-04-4P, Nateglinide

RL: PEP (Physical, engineering or chemical process); PYP

(Physical process); RCT (Reactant); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study);

PREP (Preparation); PROC (Process); RACT (Reactant or

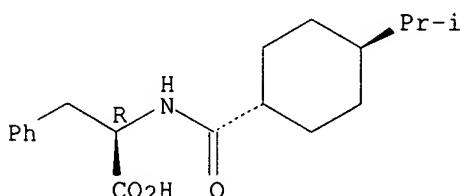
reagent); USES (Uses)

(preparation of polymorphic forms of nateglinide)

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 105816-04-4DP, Nateglinide, polymorphs

RL: PEP (Physical, engineering or chemical process); PYP

(Physical process); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation);

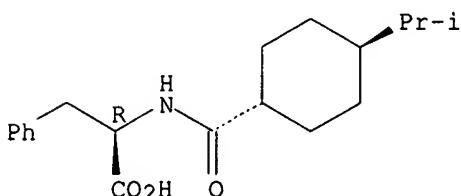
PROC (Process); USES (Uses)

(preparation of polymorphic forms of nateglinide)

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 6 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2004:41431 HCAPLUS  
 DN 140:94292  
 ED Entered STN: 18 Jan 2004  
 TI Process for preparing nateglinide and its intermediates  
 IN Yahalom, Ronit; Shapiro, Evgeny; Dolitzky,  
 Ben-zion; Gozlan, Yigael  
 PA Teva Pharmaceutical Industries Ltd., Israel; Teva  
 Pharmaceuticals Usa, Inc.  
 SO PCT Int. Appl., 31 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM C07C0231-02  
 ICS C07C0231-24; C07C0233-63; C07C0051-60; C07C0061-08  
 CC 34-2 (Amino Acids, Peptides, and Proteins)  
 Section cross-reference(s): 1, 63

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004005240	A1	20040115	WO 2003-US21238	20030703 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG				
	AU 2003256454	A1	20040123	AU 2003-256454	20030703 <--
	EP 1487782	A1	20041222	EP 2003-763310	20030703 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	CN 1671649	A	20050921	CN 2003-817439	20030703 <--
	US 2004116526	A1	20040617	US 2003-623237	20030718 <--
	US 2005014949	A1	20050120	US 2003-623290	20030718 <--
	US 2005075400	A1	20050407	US 2003-622999	20030718 <--
	CN 1723190	A	20060118	CN 2003-821921	20030718 <--
PRAI	US 2002-393495P	P	20020703	<--	
	US 2002-396904P	P	20020718	<--	
	US 2002-413622P	P	20020925	<--	
	US 2002-414199P	P	20020926	<--	
	US 2002-423750P	P	20021105	<--	
	US 2002-432093P	P	20021210	<--	
	US 2002-432962P	P	20021212	<--	
	US 2003-442109P	P	20030123		
	US 2003-449791P	P	20030224		
	US 2003-479016P	P	20030616		
	WO 2003-US21238	W	20030703		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004005240	ICM	C07C0231-02
	ICS	C07C0231-24; C07C0233-63; C07C0051-60; C07C0061-08
	IPCI	C07C0231-02 [ICM,7]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C*]; C07C0233-63 [ICS,7]; C07C0233-00

[ICS,7,C\*]; C07C0051-60 [ICS,7]; C07C0051-58  
 [ICS,7,C\*]; C07C0061-08 [ICS,7]; C07C0061-00 [ICS,7,C\*]  
 IPCR A61K0031-16 [I,A]; A61K0031-16 [I,C\*]; A61K0031-185  
 [I,C\*]; A61K0031-198 [I,A]; C07C0051-58 [I,C\*];  
 C07C0051-60 [I,A]; C07C0231-00 [I,C\*]; C07C0231-02  
 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C\*];  
 C07C0233-63 [N,A]  
 ECLA A61K031/16; A61K031/198; C07C051/60+61/08; C07C231/02;  
 C07C231/24  
 AU 2003256454 IPCI C07C0231-02 [ICM,7]; C07C0233-63 [ICS,7]; C07C0233-00  
 [ICS,7,C\*]; C07C0051-60 [ICS,7]; C07C0051-58  
 [ICS,7,C\*]; C07C0061-08 [ICS,7]; C07C0061-00  
 [ICS,7,C\*]; C07C0231-24 [ICS,7]; C07C0231-00 [ICS,7,C\*]  
 IPCR A61K0031-16 [I,A]; A61K0031-16 [I,C\*]; A61K0031-185  
 [I,C\*]; A61K0031-198 [I,A]; C07C0051-58 [I,C\*];  
 C07C0051-60 [I,A]; C07C0231-00 [I,C\*]; C07C0231-02  
 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C\*];  
 C07C0233-63 [N,A]  
 EP 1487782 IPCI C07C0231-02 [ICM,7]; C07C0231-24 [ICS,7]; C07C0231-00  
 [ICS,7,C\*]; C07C0233-63 [ICS,7]; C07C0233-00  
 [ICS,7,C\*]; C07C0051-60 [ICS,7]; C07C0051-58  
 [ICS,7,C\*]; C07C0061-08 [ICS,7]; C07C0061-00 [ICS,7,C\*]  
 IPCR A61K0031-16 [I,A]; A61K0031-16 [I,C\*]; A61K0031-185  
 [I,C\*]; A61K0031-198 [I,A]; C07C0051-58 [I,C\*];  
 C07C0051-60 [I,A]; C07C0231-00 [I,C\*]; C07C0231-02  
 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C\*];  
 C07C0233-63 [N,A]  
 CN 1671649 IPCI C07C0231-02 [ICM,7]; C07C0231-24 [ICS,7]; C07C0231-00  
 [ICS,7,C\*]; C07C0233-63 [ICS,7]; C07C0233-00  
 [ICS,7,C\*]; C07C0051-60 [ICS,7]; C07C0051-58  
 [ICS,7,C\*]; C07C0061-08 [ICS,7]; C07C0061-00 [ICS,7,C\*]  
 IPCR A61K0031-16 [I,A]; A61K0031-16 [I,C\*]; A61K0031-185  
 [I,C\*]; A61K0031-198 [I,A]; C07C0051-58 [I,C\*];  
 C07C0051-60 [I,A]; C07C0231-00 [I,C\*]; C07C0231-02  
 [I,A]; C07C0231-24 [I,A]; C07C0233-00 [N,C\*];  
 C07C0233-63 [N,A]  
 US 2004116526 IPCI A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C\*]  
 IPCR A61K0031-16 [I,A]; A61K0031-16 [I,C\*]; A61K0031-185  
 [I,C\*]; A61K0031-198 [I,A]; C07C0231-00 [I,C\*];  
 C07C0231-02 [I,A]; C07C0231-24 [I,A]; C07C0233-00  
 [N,C\*]; C07C0233-63 [N,A]  
 NCL 514/563.000  
 ECLA A61K031/16; A61K031/198; C07C231/02; C07C231/24  
 US 2005014949 IPCI C07D0417-04 [ICM,7]; C07D0417-00 [ICM,7,C\*]  
 IPCR A61K0031-185 [I,C\*]; A61K0031-198 [I,A]  
 NCL 546/270.400  
 ECLA A61K031/198  
 US 2005075400 IPCI A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C\*];  
 C07C0233-61 [ICS,7]; C07C0233-00 [ICS,7,C\*]  
 IPCR C07C0233-00 [I,C\*]; C07C0233-63 [I,A]  
 NCL 514/563.000  
 ECLA C07C231/24; C07C233/63  
 CN 1723190 IPCI C07C0231-24 [I,A]; C07C0231-00 [I,C\*]; C07C0233-63  
 [I,A]; C07C0233-00 [I,C\*]; A61K0031-16 [I,A];  
 A61P0003-00 [I,A]  
 OS CASREACT 140:94292  
 AB A process for the preparation of nateglinide involves converting  
 trans-4-isopropylcyclohexanecarboxylic acid into the acid chloride by  
 reaction with thionyl chloride in the presence of an organic amide and  
 acylation of a suitable salt of D-phenylalanine with the acid chloride in

ST a single or two phase system or in water free of a co-solvent.

IT nateglinide prepn; isopropylcyclohexanecarboxylic acid chloride  
prep acylation phenylalanine

IT 105816-04-4P, Nateglinide  
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)  
(process for preparation of nateglinide)

IT 673-06-3, D Phenylalanine 7077-05-6, trans-4  
Isopropylcyclohexanecarboxylic acid  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(process for preparation of nateglinide)

IT 84855-54-9P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(process for preparation of nateglinide)

IT 173653-89-9  
RL: PRP (Properties)  
(properties of nateglinide hydrate)

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Ajinomoto Kk; EP 1334963 A 2003 HCPLUS

(2) Koguchi, Y; US 5463116 A 1995 HCPLUS

(3) Kumashiro, I; US 4816484 A 1989 HCPLUS

(4) Shinkai, H; JOURNAL OF MEDICINAL CHEMISTRY 1989, V32(7), P1436 HCPLUS

(5) Takahashi, D; WO 2002032854 A 2002 HCPLUS

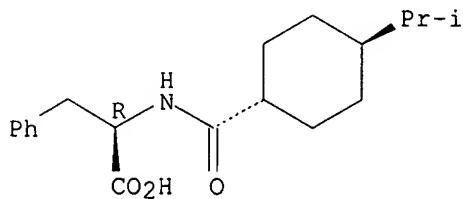
(6) Zhu, X; HECHEM HUAXUE 2001, V9(6), P537 HCPLUS

IT 105816-04-4P, Nateglinide  
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)  
(process for preparation of nateglinide)

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl)carbonyl]- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

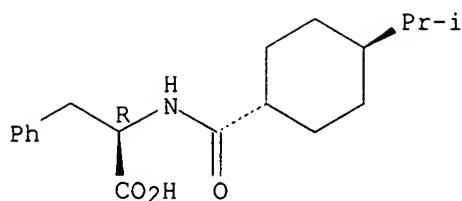


IT 173653-89-9  
RL: PRP (Properties)  
(properties of nateglinide hydrate)

RN 173653-89-9 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl)carbonyl]-, hydrate  
(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● x H<sub>2</sub>O

L61 ANSWER 7 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2003:892741 HCAPLUS  
 DN 139:369757  
 ED Entered STN: 14 Nov 2003  
 TI Process for the preparation of a crystal polymorphic form of  
 N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide)  
 IN Rajamahendra, Shanmughasamy; Aswathanarayananappa, Chandrashekhar;  
 Puthiappampil, Tom Thomas; Sridharan, Madhavan; Ganesh, Sambasivam  
 PA Biocon India Limited, India  
 SO PCT Int. Appl., 19 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM C07C0233-63  
 ICS A61K0031-198  
 CC 63-6 (Pharmaceuticals)  
 Section cross-reference(s): 34, 75  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003093222	A1	20031113	WO 2002-IN114	20020429 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2481322	AA	20031113	CA 2002-2481322	20020429 <--
	AU 2002304281	A1	20031117	AU 2002-304281	20020429 <--
	EP 1499586	A1	20050126	EP 2002-733208	20020429 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2005165108	A1	20050728	US 2003-508364	20020429 <--
	JP 2005523933	T2	20050811	JP 2004-501362	20020429 <--
PRAI	WO 2002-IN114	W	20020429 <--		
CLASS					
	PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES		
	WO 2003093222	ICM	C07C0233-63		
		ICS	A61K0031-198		

		IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; A61K0031-198 [ICS, 7]; A61K0031-185 [ICS, 7, C*]
		IPCR	A61K0031-185 [I, C*]; A61K0031-198 [I, A]; A61P0003-00 [I, C*]; A61P0003-10 [I, A]; C07B0053-00 [N, A]; C07B0053-00 [N, C*]; C07C0231-00 [I, C*]; C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]; C07C0235-00 [I, C*]; C07C0235-82 [I, A]
CA 2481322		IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; A61K0031-198 [ICS, 7]; A61K0031-185 [ICS, 7, C*]
AU 2002304281		IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; A61K0031-198 [ICS, 7]; A61K0031-185 [ICS, 7, C*]
		IPCR	A61K0031-185 [I, C*]; A61K0031-198 [I, A]; A61P0003-00 [I, C*]; A61P0003-10 [I, A]; C07B0053-00 [N, A]; C07B0053-00 [N, C*]; C07C0231-00 [I, C*]; C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]; C07C0235-00 [I, C*]; C07C0235-82 [I, A]
EP 1499586		IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; A61K0031-198 [ICS, 7]; A61K0031-185 [ICS, 7, C*]
		IPCR	A61K0031-185 [I, C*]; A61K0031-198 [I, A]; A61P0003-00 [I, C*]; A61P0003-10 [I, A]; C07B0053-00 [N, A]; C07B0053-00 [N, C*]; C07C0231-00 [I, C*]; C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]; C07C0235-00 [I, C*]; C07C0235-82 [I, A]
US 2005165108		IPCI	A61K0031-198 [ICM, 7]; A61K0031-185 [ICM, 7, C*]; C07C0235-82 [ICS, 7]; C07C0235-00 [ICS, 7, C*]
		NCL	514/563.000
JP 2005523933		IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; A61K0031-198 [ICS, 7]; A61K0031-185 [ICS, 7, C*]; A61P0003-10 [ICS, 7]; A61P0003-00 [ICS, 7, C*]; C07C0231-02 [ICS, 7]; C07C0231-24 [ICS, 7]; C07C0231-00 [ICS, 7, C*]; C07B0053-00 [ICS, 7]; C07M0007-00 [ICS, 7]
		IPCR	A61K0031-185 [I, C*]; A61K0031-198 [I, A]; A61P0003-00 [I, C*]; A61P0003-10 [I, A]; C07B0053-00 [N, A]; C07B0053-00 [N, C*]; C07C0231-00 [I, C*]; C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]; C07C0235-00 [I, C*]; C07C0235-82 [I, A]
	FTERM		4C206/AA04; 4C206/FA53; 4C206/ZC35; 4H006/AA01; 4H006/AA02; 4H006/AA03; 4H006/AB27; 4H006/AB84; 4H006/AC53; 4H006/AC81; 4H006/AD15; 4H006/BA92; 4H006/BB12; 4H006/BB31; 4H006/BJ20; 4H006/BS10; 4H006/BV24
AB	Novel polymorph Form C of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (I; i.e., nateglinide) is produced having a different IR spectrum and X-ray diffraction patterns (presented) from previously known forms of I.		
ST	nateglinide prepn <b>crystal</b> polymorphism; isopropylcyclohexylcarbonylphenylalanine prepn <b>crystal</b> polymorphism		
IT	Drying Filtration (in a process for the preparation of a <b>crystal</b> polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))		
IT	Bases, reactions RL: RGT (Reagent); RACT (Reactant or reagent) (in a process for the preparation of a <b>crystal</b> polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))		

IT Acids, reactions  
 RL: RGT (Reagent); RACT (Reactant or reagent)  
 (inorg.; in a process for the preparation of a **crystal** polymorphic  
 form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine  
 (nateglinide))

IT Diabetes mellitus  
 (non-insulin-dependent; process for the preparation of a **crystal**  
 polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-  
 phenylalanine (nateglinide) for the treatment of)

IT Antidiabetic agents  
**Polymorphism (crystal)**  
 (process for the preparation of a **crystal** polymorphic form of  
 N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT Ligroine  
 RL: NUU (Other use, unclassified); USES (Uses)  
 (solvent; process for the preparation of a **crystal** polymorphic  
 form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine  
 (nateglinide))

IT 1344-28-1, Alumina, uses  
 RL: NUU (Other use, unclassified); USES (Uses)  
 (base support; in a process for the preparation of a **crystal**  
 polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-  
 phenylalanine (nateglinide))

IT 110-86-1, Pyridine, reactions 121-44-8, Triethylamine, reactions  
 497-19-8, Sodium carbonate, reactions 584-08-7, Potassium carbonate  
 1310-58-3, Potassium hydroxide, reactions 1310-65-2, Lithium hydroxide  
 1310-73-2, Sodium hydroxide, reactions  
 RL: RGT (Reagent); RACT (Reactant or reagent)  
 (base; in a process for the preparation of a **crystal** polymorphic  
 form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine  
 (nateglinide))

IT 7077-05-6, trans-4-Isopropylcyclohexanecarboxylic acid 13033-84-6,  
 D-Phenylalanine methyl ester hydrochloride  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (in a process for the preparation of a **crystal** polymorphic form of  
 N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT 71760-04-8, Propanephosphonic acid anhydride  
 RL: RGT (Reagent); RACT (Reactant or reagent)  
 (mineral acid; in a process for the preparation of a **crystal**  
 polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-  
 phenylalanine (nateglinide))

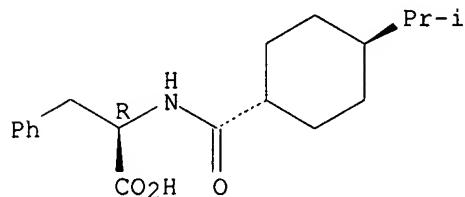
IT 105816-04-4P, Nateglinide  
 RL: IMF (Industrial manufacture); PEP (Physical,  
 engineering or chemical process); PRP (Properties); PYP  
 (Physical process); PREP (Preparation); PROC  
 (Process)  
 (process for the preparation of a **crystal** polymorphic form of  
 N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0, Isopropanol,  
 uses 75-09-2, Dichloromethane, uses 141-78-6, Ethyl acetate, uses  
 1300-21-6, Dichloroethane 7732-18-5, Water, uses  
 RL: NUU (Other use, unclassified); USES (Uses)  
 (solvent; process for the preparation of a **crystal** polymorphic  
 form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine  
 (nateglinide))

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 RE  
 (1) Ajinomoto Co Inc; EP 196222 B1 1986  
 (2) Ajinomoto Co Inc; US 4816484 A 1986 HCPLUS  
 (3) Li, G; Yaowu Fenxi Zazhi 2001, V21(5), P342 HCPLUS

(4) Shinkai, H; Journal of Medicinal Chemistry 1989, V32(7), P1436 HCPLUS  
 (5) Sumikawa; US 5463116 A 1995 HCPLUS  
 IT 105816-04-4P, Nateglinide  
 RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PREP (Preparation); PROC (Process)  
 (process for the preparation of a crystal polymorphic form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))  
 RN 105816-04-4 HCPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 8 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 2003:837030 HCPLUS  
 DN 139:341723  
 ED Entered STN: 24 Oct 2003  
 TI Novel nateglinide crystals  
 IN Koguchi, Yoshihito; Nakao, Tomoko; Sumikawa, Michito  
 PA Ajinomoto Co., Inc., Japan  
 SO PCT Int. Appl., 17 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA Japanese  
 IC ICM C07C0233-63  
 ICS C07C0231-24  
 CC 63-5 (Pharmaceuticals)  
 Section cross-reference(s): 75

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003087039	A1	20031023	WO 2003-JP4686	20030414 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003236243	A1	20031027	AU 2003-236243	20030414 <--
	EP 1496048	A1	20050112	EP 2003-746474	20030414 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	US 2005101672	A1	20050512	US 2004-965171	20041015 <--
PRAI	JP 2002-111963	A	20020415 <--		

WO 2003-JP4686

W 20030414

## CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003087039	ICM	C07C0233-63
	ICS	C07C0231-24
	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7,C*]; C07C0231-24 [ICS, 7]; C07C0231-00 [ICS, 7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	ECLA	C07C231/24; C07C233/63
AU 2003236243	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7,C*]; C07C0231-24 [ICS, 7]; C07C0231-00 [ICS, 7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
EP 1496048	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7,C*]; C07C0231-24 [ICS, 7]; C07C0231-00 [ICS, 7,C*]
	IPCR	C07C0231-00 [I,C*]; C07C0231-24 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	ECLA	C07C231/24; C07C233/63
US 2005101672	IPCI	A61K0031-198 [ICM, 7]; A61K0031-185 [ICM, 7,C*]; C07C0233-76 [ICS, 7]; C07C0233-00 [ICS, 7,C*]
	IPCR	A61K0031-185 [I,C*]; A61K0031-198 [I,A]; C07C0233-00 [I,C*]; C07C0233-76 [I,A]
	NCL	514/563.000
	ECLA	C07C233/63

AB A type **crystal** (powder X-ray diffraction main peaks:  
 $4.4^\circ$ ,  $5.2^\circ$ ,  $15.7^\circ$ ,  $18.5^\circ$  (2 theta)), M type  
**crystal** (powder X-ray diffraction main peaks:  $6.0^\circ$ ,  
 $14.2^\circ$ ,  $15.2^\circ$ ,  $18.8^\circ$  (2 theta)), and P type  
**crystal** (powder X-ray diffraction main peaks:  $4.8^\circ$ ,  
 $5.3^\circ$ ,  $14.3^\circ$ ,  $15.2^\circ$  (2 theta)) of nateglinide, which  
are all novel **crystals**, can be prepared by a method comprising  
dissolving nateglinide in a solvent exhibiting high solubility for nateglinide  
and then adding a solvent exhibiting poor solubility for nateglinide or  
dissolving nateglinide in a mixed solvent comprising a solvent exhibiting  
high solubility for nateglinide and a solvent exhibiting poor solubility for  
nateglinide and then cooling the resulting nateglinide solution to precipitate  
**crystals**, subjecting the product to filtration, and then drying at  
a specific temperature. Nateglinide is a known antidiabetic.

ST nateglinide **crystal** prepn antidiabetic

IT **Crystal structure**

(**crystal structure of nateglinide crystals**)

IT Antidiabetic agents

**Crystal structure types**

Drying

**Polymorphism (crystal)**

(preparation of A, M, and P type nateglinide **crystals** and drying  
of said **crystals**)

IT **Crystallization**

(preparation of A, M, and P type nateglinide **crystals** by  
**crystallization** from mixture of solvents)

IT 105816-04-4P, Nateglinide

RL: PRP (Properties); PUR (Purification or recovery); THU  
(Therapeutic use); BIOL (Biological study); PREP (Preparation);  
USES (Uses)

(preparation of A, M, and P type nateglinide **crystals** by  
**crystallization** from mixture of solvents)

IT 64-17-5, Ethanol, uses 67-64-1, Acetone, uses 75-09-2, Methylene  
chloride, uses 110-54-3, Hexane, uses 123-91-1, Dioxane, uses

7732-18-5, Water, uses

RL: NUU (Other use, unclassified); USES (Uses)  
 (solvent for crystallization; preparation of A, M, and P type nateglinide  
 crystals by crystallization from mixture of solvents)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Ajinomoto Co Inc; JP 05-208943 A 1993 HCPLUS
- (2) Ajinomoto Co Inc; BR 1100807 A3 1993
- (3) Ajinomoto Co Inc; ES 2100291 T3 1993 HCPLUS
- (4) Ajinomoto Co Inc; CA 2114678 A 1993 HCPLUS
- (5) Ajinomoto Co Inc; EP 526171 A2 1993 HCPLUS
- (6) Ajinomoto Co Inc; US 5463116 A 1993 HCPLUS
- (7) Ajinomoto Co Inc; US 5488150 A 1993 HCPLUS
- (8) Ajinomoto Co Inc; DE 69217762 E 1993
- (9) Ajinomoto Co Inc; WO 0234713 A1 2002 HCPLUS
- (10) Anon; AU 200196001 A

IT 105816-04-4P, Nateglinide

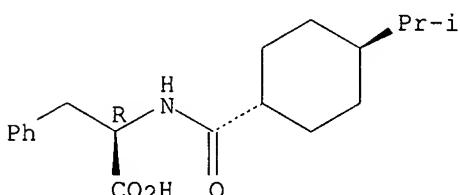
RL: PRP (Properties); PUR (Purification or recovery); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation);  
 USES (Uses)

(preparation of A, M, and P type nateglinide crystals by  
 crystallization from mixture of solvents)

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 9 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN

AN 2003:837029 HCPLUS

DN 139:328379

ED Entered STN: 24 Oct 2003

TI Crystal polymorphism of nateglinide

IN Sutton, Paul Allen

PA Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.

SO PCT Int. Appl., 10 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07C0233-63

ICS C07C0231-22

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 34, 75

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003087038	A1	20031023	WO 2003-EP3864	20030414 <--
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU,			

LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC,  
 SE, SG, SK, TJ, TM, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW  
 RW: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE,  
 DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,  
 SI, SK, TR  
 CA 2482669 AA 20031023 CA 2003-2482669 20030414 <--  
 AU 2003242520 A1 20031027 AU 2003-242520 20030414 <--  
 EP 1497258 A1 20050119 EP 2003-746296 20030414 <--  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK  
 BR 2003009210 A 20050209 BR 2003-9210 20030414 <--  
 CN 1646481 A 20050727 CN 2003-808436 20030414 <--  
 JP 2005522503 T2 20050728 JP 2003-583994 20030414 <--  
 US 2005256336 A1 20051117 US 2004-510927 20041102 <--  
 PRAI US 2002-372625P P 20020415 <--  
 WO 2003-EP3864 W 20030414

## CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003087038	ICM	C07C0233-63
	ICS	C07C0231-22
	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0231-22 [ICS, 7]; C07C0231-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-22 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
	ECLA	C07C231/22; C07C233/63
CA 2482669	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0231-22 [ICS, 7]; C07C0231-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-22 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
AU 2003242520	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0231-22 [ICS, 7]; C07C0231-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-22 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
EP 1497258	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0231-22 [ICS, 7]; C07C0231-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-22 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
BR 2003009210	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0231-22 [ICS, 7]; C07C0231-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-22 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
CN 1646481	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0231-22 [ICS, 7]; C07C0231-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-22 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
JP 2005522503	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; A61P0003-10 [ICS, 7]; A61P0003-00 [ICS, 7, C*]; C07C0231-24 [ICS, 7]; C07C0231-00 [ICS, 7, C*]; A61K0031-198 [ICS, 7]; A61K0031-185 [ICS, 7, C*]; C07M0007-00 [ICS, 7]
	IPCR	C07C0231-00 [I, C*]; C07C0231-22 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
	FTERM	4C206/AA04; 4C206/FA53; 4C206/NA20; 4C206/ZC35; 4H006/AA01; 4H006/AA02; 4H006/AB27; 4H006/AD15; 4H006/BB11; 4H006/BB14; 4H006/BC51; 4H006/BJ20; 4H006/BJ50; 4H006/BS10; 4H006/BT22
US 2005256336	IPCI	A61K0031-195 [ICM, 7]; A61K0031-185 [ICM, 7, C*]; C07C0235-70 [ICS, 7]; C07C0235-00 [ICS, 7, C*]
	IPCR	A61K0031-185 [I, C*]; A61K0031-195 [I, A]; C07C0235-00

[I,C\*]; C07C0235-70 [I,A]

NCL 562/450.000

AB New **crystal** forms of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (i.e., nateglinide) are produced by dissolving nateglinide in any of its forms, including solvates, in an organic solvent to form a solution followed by precipitation of nateglinide from the solution, and isolating and drying the precipitated **crystal** form of nateglinide. The precipitation of nateglinide may be induced either by cooling the solution, or by addition of another solvent which is miscible with the first solvent but in which nateglinide is only poorly soluble, or by combination of the two. Depending on the solvent a specific **crystal** form of nateglinide may be obtained, e.g., the R'-type **crystal** form of nateglinide produced by the described method has a different m.p., infra red spectra and X-ray diffraction patterns from the previously known **crystal** forms of nateglinide.

ST nateglinide **crystal** polymorphismIT Polymorphism (**crystal**)

(crystal polymorphism of nateglinide)

IT Cooling

Drying

Precipitation (chemical)

(in producing the **crystal** polymorphism of nateglinide)

IT Mixing

(stirring; in producing the **crystal** polymorphism of nateglinide)

IT 105816-04-4, Nateglinide

RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)  
(crystal polymorphism of nateglinide)

IT 7732-18-5, Water, uses 9004-65-3, Hydroxypropylmethylcellulose

RL: NUU (Other use, unclassified); USES (Uses)

(nonsolvent; in the **crystal** polymorphism of nateglinide)

IT 64-17-5, Ethanol, uses 108-88-3, Toluene, uses

RL: NUU (Other use, unclassified); USES (Uses)

(solvent; in the **crystal** polymorphism of nateglinide)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Alembic Ltd; WO 03022251 A 2003 HCPLUS
- (2) LI, G; YAOXUE XUEBAO 2001, V36(7), P532 HCPLUS
- (3) Sumikawa, M; US 5463116 A 1995 HCPLUS

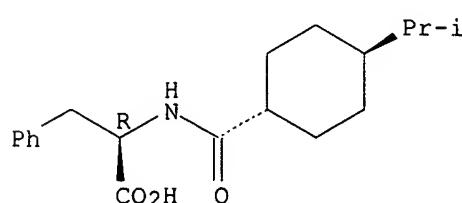
IT 105816-04-4, Nateglinide

RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)  
(crystal polymorphism of nateglinide)

RN 105816-04-4 HCPLUS

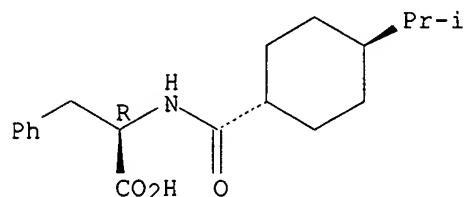
CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 10 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 2003:762699 HCPLUS  
 DN 140:64875  
 ED Entered STN: 30 Sep 2003  
 TI Study of nateglinide polymorphism  
 AU Li, Gang; Xu, Qunwei; Yao, Jie; Su, Guoqiang; Wang, Fang  
 CS Chemistry and Physics Central- laboratory, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China  
 SO Huagong Shikan (2002), 16(7), 17-18  
 CODEN: HUSHFT; ISSN: 1002-154X  
 PB Huagong Shikan Zazhishe  
 DT Journal  
 LA Chinese  
 CC 63-5 (Pharmaceuticals)  
 AB The crystal structure of nateglinide called an S form determined by an x-ray powder diffraction method. The pattern, data, and crystal size were obtained. The m.p. was determined by DSC as 172.04°.  
 ST nateglinide polymorphism crystal structure  
 IT Polymorphism (crystal)  
     (nateglinide polymorphism)  
 IT Crystal structure  
     (of nateglinide polymorph)  
 IT 105816-04-4, Nateglinide  
 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
     (nateglinide polymorphism)  
 IT 105816-04-4, Nateglinide  
 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
     (nateglinide polymorphism)  
 RN 105816-04-4 HCPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
     (CA INDEX NAME)

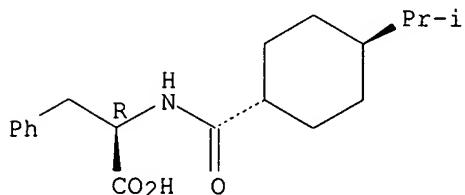
Absolute stereochemistry. Rotation (-).



L61 ANSWER 11 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 2003:686087 HCPLUS  
 DN 140:292376  
 ED Entered STN: 03 Sep 2003  
 TI Study on the crystal types of nateglinide  
 AU Sun, Piaoyang; Gou, Shaohua; Ma, Yonglin  
 CS State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing, 210093, Peop. Rep. China  
 SO Huaxue Yanjiu Yu Yingyong (2002), 14(4), 457-458, C3  
 CODEN: HYYIFM; ISSN: 1004-1656  
 PB Huaxue Yanjiu Yu Yingyong Bianjibu  
 DT Journal

LA Chinese  
 CC 63-5 (Pharmaceuticals)  
 AB N-(trans-4-methylethylcyclohexylcarbonyl)-D-phenylalanine, nateglinide, is an effective drug to decrease blood sugar, which is under clin. trials in China. This compound has been reported to have two **crystal** types, one of which is more suitable to prepare the drug. The nateglide with different **crystal** types was prepared. Their m.ps., TGA-DTA and DSC spectral data, LR and X-ray powder diffraction spectra of all samples were studied with different **crystal** types. A new **crystal** type that has not been reported in the literature was discovered. The method for controlling the **crystal** type was also presented.  
 ST nateglide polymorphism antidiabetic  
 IT Antidiabetic agents  
     Crystal morphology  
     Crystal structure  
 Human  
     Polymorphism (crystal)  
     (polymorphism of nateglinide)  
 IT 105816-04-4, Nateglinide  
     RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
     (polymorphism; polymorphism of nateglinide)  
 IT 105816-04-4, Nateglinide  
     RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
     (polymorphism; polymorphism of nateglinide)  
 RN 105816-04-4 HCAPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



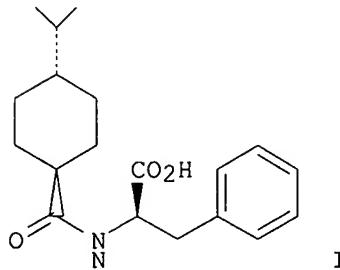
L61 ANSWER 12 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2003:221492 HCAPLUS  
 DN 138:243310  
 ED Entered STN: 21 Mar 2003  
 TI Novel stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine and process of preparation  
 IN Shah, Vrajesh; Hitkari, Anurag; Deo, Keshav; Rengaraju, Srinivasan  
 PA Alembic Limited, India  
 SO PCT Int. Appl., 25 pp.  
     CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM A61K0009-14  
     ICS A61K0009-16; C07C0229-00  
 CC 63-6 (Pharmaceuticals)  
 FAN.CNT 1  
 PATENT NO.                    KIND                    DATE                    APPLICATION NO.                    DATE  
 -----                    -----                    -----                    -----                    -----                    -----

PI	WO 2003022251	A1	20030320	WO 2001-IB2080	20011105 <--
	W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, ES, GD, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PH, PL, RO, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	IN 191354	A	20031129	IN 2001-MU872	20010912 <--
	EP 1435912	A1	20040714	EP 2001-978760	20011105 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	IN 2001-MU871	A	20010912	<--	
	IN 2001-MU872	A	20010912	<--	
	WO 2001-IB2080	W	20011105	<--	

## CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003022251	ICM	A61K0009-14
	ICS	A61K0009-16; C07C0229-00
	IPCI	A61K0009-14 [ICM, 7]; A61K0009-16 [ICS, 7]; C07C0229-00 [ICS, 7]
	IPCR	C07C0233-00 [I,C*]; C07C0233-63 [I,A]
	ECLA	C07C233/63
IN 191354	IPCI	C07C0101-34 [ICM, 7]; A61K0031-195 [ICS, 7]; A61K0031-185 [ICS, 7,C*]
EP 1435912	IPCI	A61K0009-14 [ICM, 7]; A61K0009-16 [ICS, 7]; C07C0229-00 [ICS, 7]
	IPCR	C07C0233-00 [I,C*]; C07C0233-63 [I,A]

GI



AB A stable **crystal** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (I) may be produced by **crystallization** of I with a solvent at 25 - 38 °C and forming **crystals** in the solvent. The **crystal** form may be formed by **recrystn.** out of solution. The **crystal** form obtained in this way have different m.p., infra red spectrum and X-ray diffraction patterns from previously known forms "B-type" and "H-Type" of the compound phenylalanine isopropylcyclohexylcarbonyl **crystal** form

ST **Crystal structure**  
(of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

IT **Crystal morphology**  
(stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

IT 105816-04-4  
RL: PEP (Physical, engineering or chemical process); PRP

(Properties); PYP (Physical process); THU (Therapeutic use);  
 BIOL (Biological study); PROC (Process); USES (Uses)  
 (stable crystal form of N-trans-4-  
 isopropylcyclohexylcarbonyl)-D-phenylalanine)

IT 68-12-2, Dmf, processes 75-05-8, Acetonitrile, processes 127-19-5,  
 Dimethylacetamide  
 RL: PEP (Physical, engineering or chemical process); PYP (Physical  
 process); PROC (Process)  
 (stable crystal form of N-trans-4-  
 isopropylcyclohexylcarbonyl)-D-phenylalanine)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Sumikawa; US 5463116 A 1995 HCPLUS

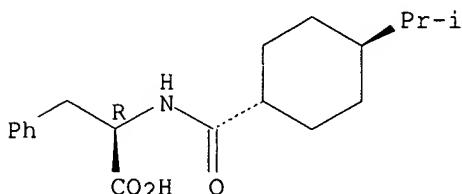
IT 105816-04-4

RL: PEP (Physical, engineering or chemical process); PRP  
 (Properties); PYP (Physical process); THU (Therapeutic use);  
 BIOL (Biological study); PROC (Process); USES (Uses)  
 (stable crystal form of N-trans-4-  
 isopropylcyclohexylcarbonyl)-D-phenylalanine)

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 13 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN

AN 2003:62632 HCPLUS

DN 138:73015

ED Entered STN: 28 Jan 2003

TI Synthesis process for trans-4-isopropylcyclohexanecarboxylic acid

IN Gu, Lianquan; An, Linkun; Ma, Lin; Guo, Xindong; Huang, Zhishu

PA Zhongshan Univ., Peop. Rep. China

SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 6 pp.

CODEN: CNXXEV

DT Patent

LA Chinese

IC ICM C07C0061-08

ICS C07C0051-36

CC 24-5 (Alicyclic Compounds)

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN 1319583	A	20011031	CN 2001-107459	20010116 <--
PRAI CN 2001-107459		20010116	<--	

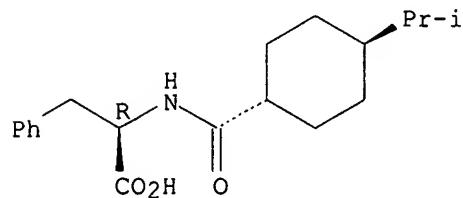
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
CN 1319583	ICM	C07C0061-08
	ICS	C07C0051-36
	IPCI	C07C0061-08 [ICM,7]; C07C0061-00 [ICM,7,C*];

C07C0051-36 [ICS,7]; C07C0051-347 [ICS,7,C\*]  
 IPCR C07C0051-347 [I,C\*]; C07C0051-36 [I,A]; C07C0061-00  
 [I,C\*]; C07C0061-08 [I,A]

OS CASREACT 138:73015  
 AB The process comprises hydrogenating cuminic acid in acetic acid in the presence of PtO<sub>2</sub>, recovering solvent, treating with 10-35% inorg. base (such as Ba(OH)<sub>2</sub>, Mg(OH)<sub>2</sub>, KOH, or NaOH) solution at 50-150° for 10-20 h, neutralizing with HCl to pH 2, **crystallizing**, filtering, and **recrystg.** in methanol.  
 ST isopropylcyclohexanecarboxylic acid prepn  
 IT Isomerization  
 Isomerization catalysts  
 (synthesis of trans-4-isopropylcyclohexanecarboxylic acid via isomerization with base)  
 IT Bases, uses  
 RL: CAT (Catalyst use); USES (Uses)  
 (synthesis of trans-4-isopropylcyclohexanecarboxylic acid via isomerization with base)  
 IT 1309-42-8, Magnesium hydroxide 1310-58-3, Potassium hydroxide, uses 1310-73-2, Sodium hydroxide, uses 1314-15-4, Platinum dioxide 17194-00-2, Barium hydroxide  
 RL: CAT (Catalyst use); USES (Uses)  
 (synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)  
 IT 105816-04-4P, Nateglinide  
 RL: PNU (Preparation, unclassified); PREP (Preparation)  
 (synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)  
 IT 536-66-3, Cuminic acid  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)  
 IT 62067-45-2P, 4-Isopropylcyclohexanecarboxylic acid  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)  
 IT 7077-05-6P, trans-4-Isopropylcyclohexanecarboxylic acid  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)  
 IT 105816-04-4P, Nateglinide  
 RL: PNU (Preparation, unclassified); PREP (Preparation)  
 (synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)  
 RN 105816-04-4 HCAPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 14 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2002:813874 HCAPLUS  
 DN 137:311199  
 ED Entered STN: 25 Oct 2002  
 TI Amino acid complexes of C-aryl glucosides for treatment of diabetes  
 IN Gougoutas, Jack Z.  
 PA Bristol-Myers Squibb Company, USA  
 SO PCT Int. Appl., 80 pp.  
 CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K

CC 34-2 (Amino Acids, Peptides, and Proteins)  
 Section cross-reference(s): 1, 33, 63, 75

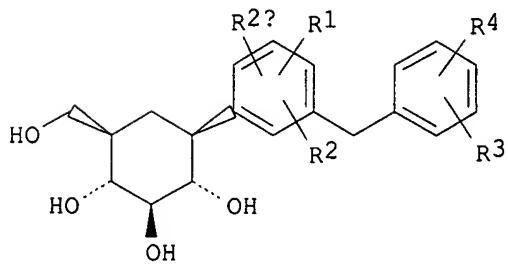
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002083066	A2	20021024	WO 2002-US11066	20020408 <--
	WO 2002083066	A3	20030306		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2444481	AA	20021024	CA 2002-2444481	20020408 <--
	US 2003064935	A1	20030403	US 2002-117914	20020408 <--
	US 6774112	B2	20040810		
	EP 1385856	A2	20040204	EP 2002-723801	20020408 <--
	EP 1385856	B1	20060222		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2004536047	T2	20041202	JP 2002-580871	20020408 <--
	AT 318272	E	20060315	AT 2002-723801	20020408 <--
PRAI	US 2001-283097P	P	20010411 <--		
	WO 2002-US11066	W	20020408 <--		

CLASS

	PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
CA 2444481	WO 2002083066	ICM	A61K
		IPCI	A61K [ICM, 7]
		IPCR	A61K0031-351 [I, A]; A61K0031-351 [I, C*]; A61K0045-00 [I, C*]; A61K0045-06 [I, A]; C07D0309-00 [I, C*]; C07D0309-10 [I, A]; C07H0015-00 [I, C*]; C07H0015-203 [I, A]
		ECLA	A61K031/351+M; A61K045/06; C07H015/203
US 2003064935		IPCI	C07H0007-04 [ICM, 7]; C07H0007-00 [ICM, 7, C*]; A61K0031-70 [ICS, 7]
		IPCR	A61K0031-351 [I, A]; A61K0031-351 [I, C*]; A61K0045-00 [I, C*]; A61K0045-06 [I, A]; C07D0309-00 [I, C*]; C07D0309-10 [I, A]; C07H0015-00 [I, C*]; C07H0015-203 [I, A]
		ECLA	A61K031/351+M; A61K045/06; C07H015/203
		IPCI	A61K0031-70 [ICM, 7]; C07H0005-06 [ICS, 7]; C07H0005-00 [ICS, 7, C*]
	IPCR	A61K0031-351 [I, A]; A61K0031-351 [I, C*]; A61K0045-00	

[I,C\*]; A61K0045-06 [I,A]; C07H0015-00 [I,C\*];  
 C07H0015-203 [I,A]  
 NCL 514/023.000  
 ECLA A61K031/351+M; A61K045/06; C07H015/203  
 EP 1385856 IPCI C07H0007-00 [I,C]; A61K0031-70 [I,C]; C07H0007-04  
 [I,A]; A61K0031-70 [I,A]  
 IPCR A61K0031-351 [I,C\*]; A61K0045-00 [I,C\*]; C07D0309-00  
 [I,C\*]; C07H0015-00 [I,C\*]; A61K0031-351 [I,A];  
 A61K0045-06 [I,A]; C07D0309-10 [I,A]; C07H0015-203  
 [I,A]  
 ECLA A61K031/351+M; A61K045/06; C07H015/203  
 JP 2004536047 IPCI C07H0007-04 [ICM,7]; C07H0007-00 [ICM,7,C\*];  
 A61K0031-7004 [ICS,7]; A61P0003-04 [ICS,7]; A61P0003-06  
 [ICS,7]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C\*];  
 A61P0009-10 [ICS,7]; A61P0009-12 [ICS,7]; A61P0009-00  
 [ICS,7,C\*]; A61P0013-12 [ICS,7]; A61P0013-00  
 [ICS,7,C\*]; A61P0017-02 [ICS,7]; A61P0017-00  
 [ICS,7,C\*]; A61P0027-02 [ICS,7]; A61P0027-00 [ICS,7,C\*]  
 IPCR A61K0031-351 [I,A]; A61K0031-351 [I,C\*]; A61K0045-00  
 [I,C\*]; A61K0045-06 [I,A]; C07D0309-00 [I,C\*];  
 C07D0309-10 [I,A]; C07H0015-00 [I,C\*]; C07H0015-203  
 [I,A]  
 FTERM 4C057/BB02; 4C057/DD01; 4C057/EE04; 4C086/AA01;  
 4C086/AA02; 4C086/AA03; 4C086/EA01; 4C086/GA15;  
 4C086/MA01; 4C086/MA02; 4C086/MA04; 4C086/MA05;  
 4C086/MA06; 4C086/MA10; 4C086/NA14; 4C086/ZA42;  
 4C086/ZA70; 4C086/ZA81; 4C086/ZA89; 4C086/ZC33;  
 4C086/ZC35  
 AT 318272 IPCI C07H0007-04 [ICS,7]; C07H0007-00 [ICM,7,C\*];  
 A61K0031-70 [ICS,7]  
 IPCR A61K0031-351 [I,C\*]; A61K0045-00 [I,C\*]; C07D0309-00  
 [I,C\*]; C07H0015-00 [I,C\*]; A61K0031-351 [I,A];  
 A61K0045-06 [I,A]; C07D0309-10 [I,A]; C07H0015-203  
 [I,A]  
 ECLA A61K031/351+M; A61K045/06; C07H015/203  
 OS MARPAT 137:311199  
 GI



AB **Crystalline** complexes are obtained from 1:1 or 2:1 mixts. of either  
 the (D) or (L) enantiomer of natural amino acids and compds. of formula I  
 [R1, R2, R2a = H, OH, OR5, alkyl, OCHF2, OCF3, SR5a, halogen; R3, R4 = H,  
 OH, OR5b, alkyl, cycloalkyl, CF3, OCHF2, OCF3, halogen, CONR6R6a, CO2R5c,  
 CO2H, COR6b, CH(OH)R6c, CH(OR5d)R6d, CN, NHCOR5e, NHSO2R5f, NHSO2-aryl,  
 SR5g, SOR5h, SO2R5i, or a five, six or seven membered heterocycle which  
 may contain 1 to 4 heteroatoms (N, O, S, SO, and/or SO2), or R3 and R4

together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring; R5, R5a-R5i are independently alkyl; R6, R6a-R6d are independently H, alkyl, aryl, alkylaryl or cycloalkyl, or NR6R6a form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring]. A method is also provided for treating diabetes and related diseases employing an SGLT2 (sodium dependent glucose transporters found in the intestine and kidney) inhibiting amount of the above complex alone or in combination with another antidiabetic agent or other therapeutic agent. Thus, I (R1 = 4-Me, R4 = 4-OCHF<sub>2</sub>, R2, R2a, R3 = H) was prepared by a multistep procedure starting from o-toluic acid, anisole, 2,3,4,6-tetra-O-benzyl- $\beta$ -D-glucolactone, and CHF<sub>2</sub>Cl and treated with L-phenylalanine to form the **crystalline** 1:1 complex.

ST **crystal structure** amino acid complex aryl glucoside; amino acid complex aryl glucoside prepn antidiabetic

IT Antiarteriosclerotics  
(antiatherosclerotics; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Wound healing  
(delayed; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Kidney, disease  
(diabetic nephropathy; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Nerve, disease  
(diabetic neuropathy; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Eye, disease  
(diabetic retinopathy; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Fatty acids, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(elevated blood levels; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Metabolic disorders  
(metabolic syndrome X; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT Antidiabetic agents  
Antiobesity agents  
Atherosclerosis  
    **Crystal structure**  
Diabetes mellitus  
Human  
Hyperglycemia  
Hypertension  
Hypertriglyceridemia  
Hypolipemic agents  
Obesity  
    (preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT High-density lipoproteins  
Hyperlipidemia  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
    (preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT 56-81-5, Glycerol, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
    (elevated blood levels; preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT 472968-85-7P 472968-86-8P 472968-87-9P 472968-88-0P 472968-89-1P  
 472968-90-4P 472968-91-5P 472968-93-7P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT 75-45-6, Freon 22 100-66-3, Anisole, reactions 100-68-5, Thioanisole 118-90-1, o Toluic acid 1585-07-5, p-Bromoethylbenzene 3132-99-8, m Bromobenzaldehyde 13096-62-3  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

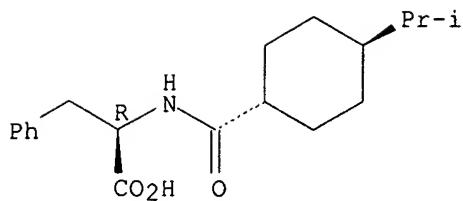
IT 79669-49-1P 333359-79-8P 333359-87-8P 333359-88-9P 333360-85-3P  
 333360-86-4P 333360-87-5P 333360-88-6P 333361-13-0P 333361-15-2P  
 333361-21-0P 333361-30-1P 333361-33-4P 333361-35-6P 333361-37-8P  
 472968-94-8P 472968-95-9P 472968-96-0P 472968-97-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT 51-64-9, Dexamphetamine 94-20-2, Chlorpropamide 122-09-8, Phentermine 637-07-0, Clofibrate 657-24-9, Metformin 9004-10-8, Insulin, biological studies 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine 21187-98-4, Gliclazide 22232-71-9, Mazindol 25812-30-0, Gemfibrozil 29094-61-9, Glipizide 49562-28-9, Fenofibrate 56180-94-0, Acarbose 72432-03-2, Miglitol 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate 97322-87-7, Troglitazone 105816-04-4, Nateglinide 106650-56-0, Sibutramine 111025-46-8, Pioglitazone 122320-73-4, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 141750-63-2, Nisvastatin 141758-74-9, AC2993 144288-97-1, TS 962 145599-86-6, Cerivastatin 147511-69-1, Pitavastatin 152755-31-2, LY295427 159183-92-3, L750355 161600-01-7, Isaglitazone 166518-60-1, Avasimibe 170861-63-9, JTT-501 176435-10-2, LY315902 178759-95-0, MD 700 196808-45-4 199113-98-9, NN-2344 199914-96-0, YM-440 213252-19-8, KRP297 244081-42-3, AJ9677 282526-98-1, ATL-962 287714-41-4, Rosuvastatin 335149-08-1, L895645 335149-14-9, R-119702 335149-15-0, KAD1129 335149-17-2, ARHO39242 335149-19-4, GW-409544 335149-23-0, NVPDPP-728A 335149-25-2, CP331648 430433-17-3, Glipyride 444069-80-1, Axokine  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT 105816-04-4, Nateglinide  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

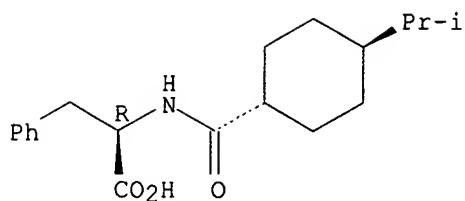
RN 105816-04-4 HCPLUS  
 CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



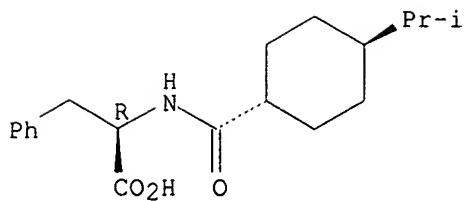
L61 ANSWER 15 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2002:811385 HCAPLUS  
 DN 139:12440  
 ED Entered STN: 25 Oct 2002  
 TI Identification of nateglinide and its **crystal** forms in  
 nateglinide tablets using IR Spectra subtraction techniques  
 AU Lin, Kejiang; Chen, Wei; Tang, Weiguo; You, Qidong  
 CS Department of Medicinal Chemistry, China Pharmaceutical University,  
 Nanjing, 21009, Peop. Rep. China  
 SO Zhongguo Yaoke Daxue Xuebao (2002), 33(2), 124-126  
 CODEN: ZHYXE9; ISSN: 1000-5048  
 PB Zhongguo Yaoke Daxue  
 DT Journal  
 LA Chinese  
 CC 64-3 (Pharmaceutical Analysis)  
 Section cross-reference(s): 63  
 AB The innovational identification method of IR (eliminated method) for  
 detection of the **crystal** form of nateglinide in preps. was  
 presented. The IR spectrum by spectra subtraction techniques was obtained  
 by subtracting IR spectrum after adding small volume of solvent to eliminate  
 nateglinide from the spectrum of nateglinide tablets' KBr disk to identify  
 the **crystal** form of nateglinide. The method (eliminated method)  
 was useful in identification of the nateglinide **crystal** form in  
 preps.  
 ST nateglinide tablet **crystal** form IR spectra  
 IT **Crystal morphology**  
 IR spectra  
 (identification of nateglinide and its **crystal** forms in  
 nateglinide tablets using IR spectra subtraction techniques)  
 IT Drug delivery systems  
 (tablets; identification of nateglinide and its **crystal** forms  
 in nateglinide tablets using IR spectra subtraction techniques)  
 IT 105816-04-4, Nateglinide  
 RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL  
 (Biological study); USES (Uses)  
 (identification of nateglinide and its **crystal** forms in  
 nateglinide tablets using IR spectra subtraction techniques)  
 IT 105816-04-4, Nateglinide  
 RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL  
 (Biological study); USES (Uses)  
 (identification of nateglinide and its **crystal** forms in  
 nateglinide tablets using IR spectra subtraction techniques)  
 RN 105816-04-4 HCAPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 16 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 2002:609152 HCPLUS  
 DN 138:254901  
 ED Entered STN: 15 Aug 2002  
 TI a new synthesis method of nateglinide as antidiabetic drug  
 AU Wang, Dun; Liang, Yiheng; Gong, Ping; Zhao, Yanfang  
 CS School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, 110016, Peop. Rep. China  
 SO Zhongguo Yaowu Huaxue Zazhi (2002), 12(2), 94-96  
 CODEN: ZYHZEF; ISSN: 1005-0108  
 PB Zhongguo Yaowu Huaxue Zazhi Bianjibu  
 DT Journal  
 LA Chinese  
 CC 25-17 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)  
 Section cross-reference(s): 63  
 OS CASREACT 138:254901  
 AB A new antidiabetic drug-nateglinide was synthesized from isopropylbenzene by Friedel-Crafts reaction, chloroform reaction, catalytic hydrogenation to obtain trans-4-isopropylhexanecarboxylic acid, acylation of D-phenylalanine Et ester, hydrolysis to obtain nateglinide B-type crystal, and crystal-conversion. The total yield was 9.8%.  
 ST nateglinide antidiabetic drug synthesis  
 IT Antidiabetic agents  
     (of nateglinide and synthesis thereof)  
 IT Crystal structure types  
     (type B; of nateglinide as antidiabetic drug)  
 IT 63-91-2, L-Phenylalanine, reactions 75-36-5, Acetyl chloride 98-82-8, Isopropylbenzene 524-38-9 3081-24-1  
     RL: RCT (Reactant); RACT (Reactant or reagent)  
     (synthesis of nateglinide as antidiabetic drug)  
 IT 536-66-3P, 4-Isopropylbenzoic acid 645-13-6P, 4-Isopropylacetophenone 7077-05-6P, trans-4-Isopropylcyclohexanecarboxylic acid 508170-82-9P  
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
     (synthesis of nateglinide as antidiabetic drug)  
 IT 105816-04-4P, Nateglinide  
     RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
     (synthesis of nateglinide as antidiabetic drug)  
 IT 105816-04-4P, Nateglinide  
     RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
     (synthesis of nateglinide as antidiabetic drug)  
 RN 105816-04-4 HCPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl)carbonyl]- (9CI)  
     (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 17 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2002:391524 HCAPLUS  
 DN 136:374894  
 ED Entered STN: 24 May 2002  
 TI Nateglinide-containing hydrophilic drug preparations  
 IN Ninomiya, Nobutaka; Makino, Chisato; Yabuki, Akira  
 PA Ajinomoto Co., Inc., Japan  
 SO PCT Int. Appl., 26 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA Japanese  
 IC ICM A61K0031-198  
 ICS A61K0009-20; A61K0009-28; A61K0047-10; A61K0047-26; A61K0047-38;  
 A61P0003-10  
 CC 63-6 (Pharmaceuticals)  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002040010	A1	20020523	WO 2001-JP9292	20011023 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU	2001096000	A5	20020527	AU 2001-96000	20011023 <--
CA	2426764	AA	20030423	CA 2001-2426764	20011023 <--
BR	2001014897	A	20030812	BR 2001-14897	20011023 <--
EP	1334721	A1	20030813	EP 2001-976818	20011023 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US	2004029968	A1	20040212	US 2003-420886	20030423 <--
PRAI	JP 2000-324374	A	20001024	<--	
	WO 2001-JP9292	W	20011023	<--	

	PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002040010	ICM	A61K0031-198	
	ICS	A61K0009-20; A61K0009-28; A61K0047-10; A61K0047-26; A61K0047-38; A61P0003-10	
	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0009-20 [ICS,7]; A61K0009-28 [ICS,7]; A61K0047-10 [ICS,7]; A61K0047-26 [ICS,7]; A61K0047-38 [ICS,7]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*]	
	IPCR	A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0031-185 [I,C*];	

		A61K0031-198 [I,A]
	ECLA	A61K009/20; A61K009/20H4B; A61K009/20H6F2; A61K009/28H6F2; A61K009/28H6D; A61K031/198
AU 2001096000	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0009-20 [ICS,7]; A61K0009-28 [ICS,7]; A61K0047-10 [ICS,7]; A61K0047-26 [ICS,7]; A61K0047-38 [ICS,7]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*]
	IPCR	A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]
CA 2426764	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0047-10 [ICS,7]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*]; A61K0009-20 [ICS,7]; A61K0047-26 [ICS,7]; A61K0009-28 [ICS,7]; A61K0047-38 [ICS,7]
BR 2001014897	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0009-20 [ICS,7]; A61K0009-28 [ICS,7]; A61K0047-10 [ICS,7]; A61K0047-26 [ICS,7]; A61K0047-38 [ICS,7]
	IPCR	A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]
EP 1334721	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; A61K0009-20 [ICS,7]; A61K0009-28 [ICS,7]; A61K0047-10 [ICS,7]; A61K0047-26 [ICS,7]; A61K0047-38 [ICS,7]; A61P0003-10 [ICS,7]; A61P0003-00 [ICS,7,C*]
	IPCR	A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]
	ECLA	A61K009/20; A61K009/20H4B; A61K009/20H6B; A61K009/20H6F2; A61K009/28H6D; A61K009/28H6F2; A61K031/198
US 2004029968	IPCI	A61K0031-198 [ICM,7]; A61K0031-185 [ICM,7,C*]; C07C0235-78 [ICS,7]; C07C0235-00 [ICS,7,C*]
	IPCR	A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0031-185 [I,C*]; A61K0031-198 [I,A]
	NCL	514/563.000
	ECLA	A61K009/20; A61K009/20H4B; A61K009/20H6B; A61K009/20H6F2; A61K009/28H6D; A61K009/28H6F2; A61K031/198

AB Hydrophilic drug preps. contain nateglinide B **crystals** useful as a hypoglycemic agent as the active ingredient which comprises a hydrophilic substance selected from the group consisting of hydrophilic polymers, surfactants, sugars, sugar alcs. and salts, and thus have a contact angle of the preparation surface to water of 111° or less. These preps., which are rapid release preps. having high elution properties, can be easily produced.

ST nateglinide drug formulation

IT **Crystals**

(hypoglycemic hydrophilic drug preps. containing nateglinide)

IT Antidiabetic agents

(nateglinide-containing hydrophilic drug preps. as)

IT Surfactants

(nateglinide-containing hydrophilic drug preps. containing)

IT Alditols

Carbohydrates, biological studies

Polymers, biological studies

Salts, biological studies

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(nateglinide-containing hydrophilic drug preps. containing)

IT Contact angle  
(of nateglinide-containing hydrophilic drug preps.)

IT 105816-04-4, Nateglinide  
RL: BCP (Biochemical process); THU (Therapeutic use); BIOL  
(Biological study); PROC (Process); USES (Uses)  
(hypoglycemic hydrophilic drug preps. containing)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

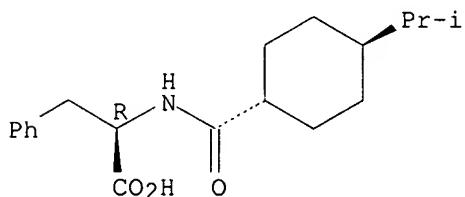
- (1) Ajinomoto Co Inc; JP 05208943 A 1993 HCAPLUS
- (2) Ajinomoto Co Inc; EP 526171 A2 1993 HCAPLUS
- (3) Ajinomoto Co Inc; US 5463116 A 1993 HCAPLUS
- (4) Ajinomoto Co Inc; US 5488150 A 1993 HCAPLUS
- (5) Ajinomoto Co Inc; JP 10194969 A 1999 HCAPLUS
- (6) Ajinomoto Co Inc; US 9143323 A 1999
- (7) Ajinomoto Co Inc; EP 965339 A1 1999 HCAPLUS
- (8) Ajinomoto Co Inc; WO 9822105 A1 1999 HCAPLUS
- (9) Nissan Chemical Industries Ltd; JP 06183955 A 1994 HCAPLUS
- (10) Shin-Etsu Chemical Co Ltd; JP 07324101 A 1995 HCAPLUS

IT 105816-04-4, Nateglinide  
RL: BCP (Biochemical process); THU (Therapeutic use); BIOL  
(Biological study); PROC (Process); USES (Uses)  
(hypoglycemic hydrophilic drug preps. containing)

RN 105816-04-4 HCAPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 18 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN

AN 2002:332157 HCAPLUS

DN 136:340998

ED Entered STN: 03 May 2002

TI Process for producing B-form nateglinide **crystals**

IN Sumikawa, Michito; Maruo, Makoto; Miyazaki, Kazuo; Nishina, Shigehiro;  
Matsuzawa, Yukiko

PA Ajinomoto Co., Inc., Japan

SO PCT Int. Appl., 9 pp.

CODEN: PIXXD2

DT Patent

LA Japanese

IC ICM C07C0233-63

ICS C07C0227-42

CC 34-2 (Amino Acids, Peptides, and Proteins)  
Section cross-reference(s): 1, 75

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002034713	A1	20020502	WO 2001-JP9293	20011023 <-- W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,  
 PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,  
 US, UZ, VN, YU, ZA, ZW  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
 BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  
 AU 2001096001 A5 20020506 AU 2001-96001 20011023 <--  
 CA 2426745 AA 20030423 CA 2001-2426745 20011023 <--  
 EP 1334964 A1 20030813 EP 2001-976819 20011023 <--  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR  
 BR 2001014846 A 20040225 BR 2001-14846 20011023 <--  
 RU 2275354 C2 20060427 RU 2003-111948 20011023 <--  
 US 2003229249 A1 20031211 US 2003-421888 20030424 <--  
 PRAI JP 2000-324375 A 20001024 <--  
 WO 2001-JP9293 W 20011023 <--  
 CLASS  
 PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002034713	ICM	C07C0233-63
	ICS	C07C0227-42
	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0227-42 [ICS, 7]; C07C0227-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [N, C*]; C07C0233-63 [N, A]
	ECLA	C07C231/24
AU 2001096001	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0227-42 [ICS, 7]; C07C0227-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [N, C*]; C07C0233-63 [N, A]
CA 2426745	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0227-42 [ICS, 7]; C07C0227-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [N, C*]; C07C0233-63 [N, A]
EP 1334964	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0227-42 [ICS, 7]; C07C0227-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [N, C*]; C07C0233-63 [N, A]
	ECLA	C07C231/24
BR 2001014846	IPCI	C07C0233-63 [ICM, 7]; C07C0233-00 [ICM, 7, C*]; C07C0227-42 [ICS, 7]; C07C0227-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [N, C*]; C07C0233-63 [N, A]
RU 2275354	IPCI	C07C0233-63 [I, A]; C07C0233-00 [I, C*]; C07C0227-42 [I, A]; C07C0227-00 [I, C*]
US 2003229249	IPCI	A61K0031-198 [ICM, 7]; A61K0031-185 [ICM, 7, C*]; C07C0235-34 [ICS, 7]; C07C0235-00 [ICS, 7, C*]
	IPCR	C07C0231-00 [I, C*]; C07C0231-24 [I, A]; C07C0233-00 [N, C*]; C07C0233-63 [N, A]
	NCL	562/450.000
	ECLA	C07C231/24

AB A process for producing B-form nateglinide crystals containing substantially no H-form crystals comprises the steps of drying wet crystals of a nateglinide solvate at a low temperature until the solvent disappears and then causing them to undergo a crystal transition. Nateglinide is a known antidiabetic. By this process, B-form nateglinide crystals can be produced on an industrial scale.

ST B form nateglinide crystal prep'n antidiabetic  
IT Crystallization

IT (crystallization of nateglinide)  
 Differential scanning calorimetry  
 (industrial process for producing B-form nateglinide crystals  
 )  
 IT 105816-04-4P, Nateglinide  
 RL: PAC (Pharmacological activity); PUR (Purification or recovery)  
 ; THU (Therapeutic use); BIOL (Biological study); PREP  
 (Preparation); USES (Uses)  
 (industrial process for producing B-form nateglinide crystals  
 )  
 IT 173653-89-9  
 RL: PEP (Physical, engineering or chemical process); PROC  
 (Process)  
 (industrial process for producing B-form nateglinide crystals  
 )

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

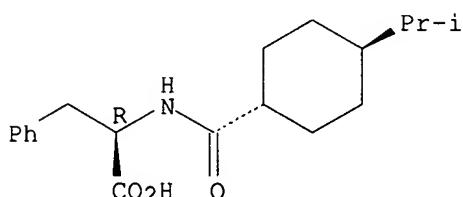
- (1) Ajinomoto Co Inc; JP 6354321 A 1988
- (2) Ajinomoto Co Inc; JP 05208943 A 1995 HCPLUS
- (3) Ajinomoto Co Inc; US 5463116 A 1995 HCPLUS

IT 105816-04-4P, Nateglinide  
 RL: PAC (Pharmacological activity); PUR (Purification or recovery)  
 ; THU (Therapeutic use); BIOL (Biological study); PREP  
 (Preparation); USES (Uses)  
 (industrial process for producing B-form nateglinide crystals  
 )

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl)carbonyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

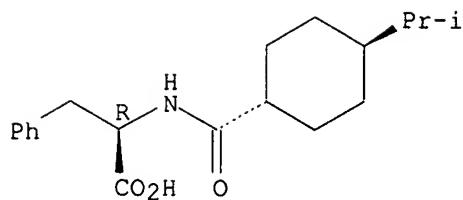


IT 173653-89-9  
 RL: PEP (Physical, engineering or chemical process); PROC  
 (Process)  
 (industrial process for producing B-form nateglinide crystals  
 )

RN 173653-89-9 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl)carbonyl]-, hydrate  
 (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● x H<sub>2</sub>O

L61 ANSWER 19 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2002:314896 HCAPLUS  
 DN 136:325825  
 ED Entered STN: 26 Apr 2002  
 TI Process for producing nateglinide **crystals**  
 IN Takahashi, Daisuke; Nishi, Seiichi; Takahashi, Satoji  
 PA Ajinomoto Co., Inc., Japan  
 SO PCT Int. Appl., 14 pp.  
 CODEN: PIIXD2  
 DT Patent  
 LA Japanese  
 IC ICM C07C0231-24  
 ICS C07C0231-02; C07C0233-63  
 CC 34-2 (Amino Acids, Peptides, and Proteins)  
 Section cross-reference(s): 1, 75

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002032854	A1	20020425	WO 2001-JP9069	20011016 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU	2001094265	A5	20020429	AU 2001-94265	20011016 <--
CA	2425538	AA	20030410	CA 2001-2425538	20011016 <--
EP	1334963	A1	20030813	EP 2001-974875	20011016 <--
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BR	2001014729	A	20031014	BR 2001-14729	20011016 <--
RU	2273629	C2	20060410	RU 2003-111021	20011016 <--
CN	1769263	A	20060510	CN 2005-10118852	20011016 <--
US	2004030182	A1	20040212	US 2003-418105	20030418 <--
PRAI	JP 2000-317604	A	20001018	<--	
	CN 2001-820658	A3	20011016	<--	
	WO 2001-JP9069	W	20011016	<--	

CLASS

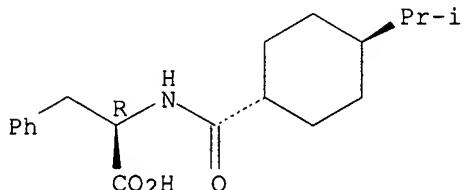
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002032854	ICM	C07C0231-24

ICS C07C0231-02; C07C0233-63  
 IPCI C07C0231-24 [ICM, 7]; C07C0231-02 [ICS, 7]; C07C0231-00  
       [ICS, 7, C\*]; C07C0233-63 [ICS, 7]; C07C0233-00 [ICS, 7, C\*]  
 IPCR C07C0231-00 [I, C\*]; C07C0231-02 [I, A]; C07C0231-24  
       [I, A]; C07C0233-00 [N, C\*]; C07C0233-63 [N, A]  
 ECLA C07C231/02; C07C231/24  
 AU 2001094265 IPCI C07C0231-24 [ICM, 7]; C07C0231-02 [ICS, 7]; C07C0231-00  
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 IPCR C07C0231-00 [I, C\*]; C07C0231-02 [I, A]; C07C0231-24  
       [I, A]; C07C0233-00 [N, C\*]; C07C0233-63 [N, A]  
 CA 2425538 IPCI C07C0231-24 [ICM, 7]; C07C0231-02 [ICS, 7]; C07C0231-00  
       [ICS, 7, C\*]; C07C0233-63 [ICS, 7]; C07C0233-00 [ICS, 7, C\*]  
 IPCR C07C0231-00 [I, C\*]; C07C0231-02 [I, A]; C07C0231-24  
       [I, A]; C07C0233-00 [N, C\*]; C07C0233-63 [N, A]  
 EP 1334963 IPCI C07C0231-24 [ICM, 7]; C07C0231-02 [ICS, 7]; C07C0231-00  
       [ICS, 7, C\*]; C07C0233-63 [ICS, 7]; C07C0233-00 [ICS, 7, C\*]  
 IPCR C07C0231-00 [I, C\*]; C07C0231-02 [I, A]; C07C0231-24  
       [I, A]; C07C0233-00 [N, C\*]; C07C0233-63 [N, A]  
 ECLA C07C231/02; C07C231/24  
 BR 2001014729 IPCI C07C0231-24 [ICM, 7]; C07C0231-02 [ICS, 7]; C07C0231-00  
       [ICS, 7, C\*]; C07C0233-63 [ICS, 7]; C07C0233-00 [ICS, 7, C\*]  
 IPCR C07C0231-00 [I, C\*]; C07C0231-02 [I, A]; C07C0231-24  
       [I, A]; C07C0233-00 [N, C\*]; C07C0233-63 [N, A]  
 RU 2273629 IPCI C07C0231-24 [I, A]; C07C0231-02 [I, A]; C07C0231-00  
       [I, C\*]; C07C0233-63 [I, A]; C07C0233-00 [I, C\*]  
 CN 1769263 IPCI C07C0231-02 [I, A]; C07C0231-24 [I, A]; C07C0231-00  
       [I, C\*]; C07C0233-63 [I, A]; C07C0233-00 [I, C\*]  
 US 2004030182 IPCI C07C0231-02 [ICM, 7]; C07C0231-00 [ICM, 7, C\*]  
 IPCR C07C0231-00 [I, C\*]; C07C0231-02 [I, A]; C07C0231-24  
       [I, A]; C07C0233-00 [N, C\*]; C07C0233-63 [N, A]  
 NCL 562/450.000

OS CASREACT 136:325825  
 AB A process for producing nateglinide **crystals** comprises reacting  
       trans-4-isopropylcyclohexylcarbonyl chloride with D-phenylalanine in a  
       mixed solvent consisting of a ketone solvent and water in the presence of  
       an alkali to obtain a reaction mixture containing nateglinide, adding an acid  
 to  
       the reaction mixture to make it acidic, and regulating (a) the temperature to  
       58° to 72° and (b) and the ketone solvent concentration to > 8 weight%  
       and < 22 weight%, to conduct **crystallization**. Nateglinide is a known  
       antidiabetic. The process is an industrially advantageous method for  
       **crystallizing** nateglinide.  
 ST nateglinide **crystal** prep<sup>n</sup> antidiabetic  
 IT Acylation  
       (acylation of D-phenylalanine)  
 IT Crystal structure  
       (crystal structure of nateglinide)  
 IT Crystallization  
       (process for producing nateglinide **crystals**)  
 IT Alkali metal hydroxides  
 RL: RGT (Reagent); RACT (Reactant or reagent)  
       (process for producing nateglinide **crystals**)  
 IT Ketones, uses  
 RL: NUU (Other use, unclassified); USES (Uses)  
       (solvents; process for producing nateglinide **crystals**)  
 IT 105816-04-4P, Nateglinide  
 RL: IMF (Industrial manufacture); PRP (Properties); PUR  
       (Purification or recovery); SPN (Synthetic preparation);  
       THU (Therapeutic use); BIOL (Biological study); PREP (Preparation)  
       ; USES (Uses)

IT (process for producing nateglinide **crystals**)  
 IT 673-06-3, D-Phenylalanine 84855-54-9  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (process for producing nateglinide **crystals**)  
 IT 1310-58-3, Potassium hydroxide, reactions 7647-01-0, Hydrochloric acid, reactions  
 RL: RGT (Reagent); RACT (Reactant or reagent)  
 (process for producing nateglinide **crystals**)  
 IT 67-64-1, Acetone, uses 7732-18-5, Water, uses  
 RL: NUU (Other use, unclassified); USES (Uses)  
 (solvent; process for producing nateglinide **crystals**)  
 RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 RE  
 (1) Ajinomoto Co; EP 196222 A2 1986  
 (2) Ajinomoto Co; JP 6354321 A 1986  
 (3) Ajinomoto Co; JP 05208943 A 1993 HCPLUS  
 (4) Ajinomoto Co; EP 526171 A2 1993 HCPLUS  
 IT 105816-04-4P, Nateglinide  
 RL: IMF (Industrial manufacture); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (process for producing nateglinide **crystals**)  
 RN 105816-04-4 HCPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

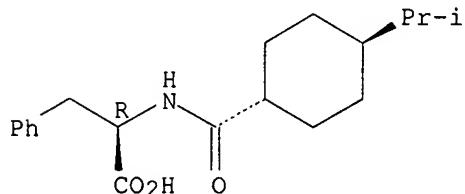


L61 ANSWER 20 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 2002:234892 HCPLUS  
 DN 137:39555  
 ED Entered STN: 28 Mar 2002  
 TI Detection of **crystal** polymorphs of nateglinide by DSC  
 AU Lin, Kejiang; Chen, Wei; You, Qidong  
 CS China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China  
 SO Yaoxue Xuebao (2002), 37(1), 46-49  
 CODEN: YHHPAL; ISSN: 0513-4870  
 PB Yaoxue Xuebao Bianjibu  
 DT Journal  
 LA Chinese  
 CC 75-7 (**Crystallography** and **Liquid Crystals**)  
 AB The differential scanning calorimetric (DSC) methodol. for controlling the **crystal**-type B form of nateglinide was presented. Pure fine powder of **crystal**-type B and H of nateglinide dried with P2O5 as desiccant at 80° in vacuum for 4 h was measured dQ/dT by DSC at heating rate of 10° min-1 and temperature between 100° and 200° to calculate the enthalpy  $\Delta H_B$  and  $\Delta H_H$ . Uniform mixts. of **crystal**-type B and H of dried fine powder of nateglinide in different proportions were accurately weighed. The enthalpy of the mixts.

was measured by DSC as above to calculate the enthalpy ( $\Delta H$ ). Using B% as X,  $\Delta H$  as parameters, the regression equation was obtained. Based on this equation, the unknown composition of mixed **crystal** was evaluated by  $y\Delta H$  values. The method was used to control the limitation of **crystal-type B** of nateglinide by the  $H\Delta H$  value of mixture of known composition as reference. The results measured from different labs. showed that the repeatability was 0.61% and recoveries were 86.2-127% when the amount of **crystal-type B** was between 0-15%. This method can be used to evaluate the **crystal-type B** composition of nateglinide.

ST nateglinide **crystal** polymorph control  
 IT **Crystal** growth  
 Differential scanning calorimetry  
 (control of polymorphism during **crystal** growth of nateglinide detected by DSC)  
 IT **Polymorphism (crystal)**  
 (detection of **crystal** polymorphs of nateglinide by DSC)  
 IT **Enthalpy**  
 (of polymorphism of nateglinide **crystals**)  
 IT 105816-04-4, Nateglinide  
 RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)  
 (detection of **crystal** polymorphs of nateglinide by DSC)  
 IT 105816-04-4, Nateglinide  
 RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)  
 (detection of **crystal** polymorphs of nateglinide by DSC)  
 RN 105816-04-4 HCAPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
 (CA INDEX NAME)

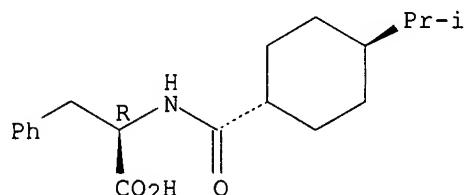
Absolute stereochemistry. Rotation (-).



L61 ANSWER 21 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2002:130037 HCAPLUS  
 DN 137:325603  
 ED Entered STN: 20 Feb 2002  
 TI Synthesis of Nateglinide  
 AU Zhu, Xue-yan; Peng, Ka; Wang, Xiao-qin; Yang, Li-ping  
 CS Dep. Chem., East China Normal Univ., Shanghai, 200062, Peop. Rep. China  
 SO Hecheng Huaxue (2001), 9(6), 537-540  
 CODEN: HEHUE2; ISSN: 1005-1511  
 PB Hecheng Huaxue Bianjibu  
 DT Journal  
 LA Chinese  
 CC 34-2 (Amino Acids, Peptides, and Proteins)  
 OS CASREACT 137:325603  
 AB Title compound, a new antidiabetes medicine, was synthesized from iso-propylbenzene in seven steps, giving the product with overall yield 22%.

ST Nateglinide synthesis isopropylbenzene antidiabetes drug  
 IT Diabetes mellitus  
     (non-insulin-dependent; of Nateglinide)  
 IT Antidiabetic agents  
     (of Nateglinide)  
 IT 7440-02-0, Raney nickel, uses  
     RL: CAT (Catalyst use); USES (Uses)  
         (catalysts; synthesis of Nateglinide)  
 IT 105816-04-4DP, Nateglinide, B crystal type  
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP  
         (Preparation); RACT (Reactant or reagent)  
         (preparation and crystalline forms of)  
 IT 98-82-8, Iso-propylbenzene 673-06-3, D-Phenylalanine 30525-89-4,  
     Paraformaldehyde  
     RL: RCT (Reactant); RACT (Reactant or reagent)  
         (synthesis of Nateglinide)  
 IT 122-03-2P 536-66-3P 2051-18-5P 7077-05-6P 62067-45-2P  
     84855-54-9P  
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
         (Reactant or reagent)  
         (synthesis of Nateglinide)  
 IT 105816-04-4DP, H crystal type  
     RL: SPN (Synthetic preparation); PREP (Preparation)  
         (synthesis of Nateglinide)  
 IT 105816-04-4DP, Nateglinide, B crystal type  
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP  
         (Preparation); RACT (Reactant or reagent)  
         (preparation and crystalline forms of)  
 RN 105816-04-4 HCAPLUS  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
     (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RL: SPN (Synthetic preparation); PREP (Preparation)  
     (synthesis of Nateglinide)

L61 ANSWER 22 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2001:844448 HCAPLUS  
 DN 136:159110  
 ED Entered STN: 21 Nov 2001  
 TI A new crystal structure in nateglinide found by X-ray powder  
     diffraction  
 AU Li, Gang; Su, Guo-qiang; Xu, Qun-wei  
 CS Center for Analysis & Measurement, Nanjing Normal University, Nanjing,  
     210097, Peop. Rep. China  
 SO Yaowu Fenxi Zazhi (2001), 21(5), 342-344  
     CODEN: YFZADL; ISSN: 0254-1793  
 PB Yaowu Fenxi Zazhi Bianji Weiyuanhui  
 DT Journal  
 LA Chinese

CC 75-8 (**Crystallography and Liquid Crystals**)  
 Section cross-reference(s): 1, 63

AB A new **crystal** structure being assigned as S-form was found in nateglinide. The x-ray pattern and data were given and the m.p. was determined. Phase anal. was carried out by x-ray powder diffraction; the m.ps. were determined by DSC. S-form nateglinide was different from the H or B **crystal** form. The m.p. was 172.04°. S-form nateglinide was a new **crystal** form. X-ray powder diffraction anal. was one of the most effective methods for phase structure characterization.

ST **crystal structure** nateglinide

IT **Crystal structure**  
 Molecular structure  
 (of nateglinide)

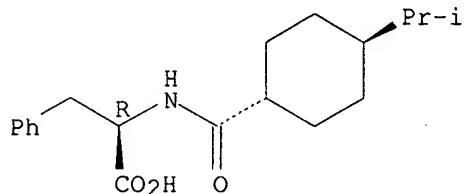
IT 105816-04-4, Nateglinide  
 RL: PRP (Properties)  
 (crystal structure of)

IT 105816-04-4, Nateglinide  
 RL: PRP (Properties)  
 (crystal structure of)

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 23 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 2001:625224 HCPLUS  
 DN 136:348527  
 ED Entered STN: 29 Aug 2001  
 TI New **crystal** form of nateglinide  
 AU Li, Gang; Su, Guoqiang; Xu, Qunwei; Zhu, Chongquan  
 CS Chemistry and Physics Central Laboratory, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China  
 SO Yaoxue Xuebao (2001), 36(7), 532-534  
 CODEN: YHHPAL; ISSN: 0513-4870  
 PB Yaoxue Xuebao Bianjibu  
 DT Journal  
 LA Chinese  
 CC 75-8 (**Crystallography and Liquid Crystals**)  
 Section cross-reference(s): 1, 34, 63

AB The S form **crystals** of nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] were studied by XRD, IR, elemental anal., and differential scan calorimetry. The S-form nateglinide **crystal** was different from the H-form or B-form. The m.p. was 172.04°. The results showed that the S-form nateglinide was a new **crystal** form.

ST nateglinide X ray **crystallog** study

IT **Crystal structure**  
 (crystal structure of nateglinide **crystals**  
 (S-form))

IT Antidiabetic agents  
(nateglinide)

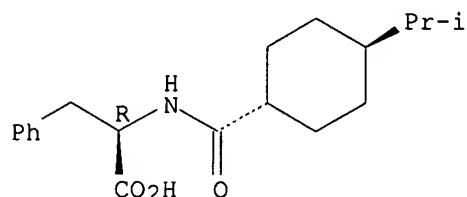
IT 105816-04-4, Nateglinide  
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(new crystal form of nateglinide)

IT 105816-04-4, Nateglinide  
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(new crystal form of nateglinide)

RN 105816-04-4 HCAPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl)carbonyl]- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L61 ANSWER 24 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
AN 2001:283772 HCAPLUS  
DN 134:285620  
ED Entered STN: 20 Apr 2001  
TI Method of treating metabolic disorders with nateglinide  
IN Gatlin, Marjorie Regan; Pongowski, Michele; Dunning, Beth  
PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.  
SO PCT Int. Appl., 28 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
IC ICM A61K0031-00  
CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1, 2

FAN.CNT 1

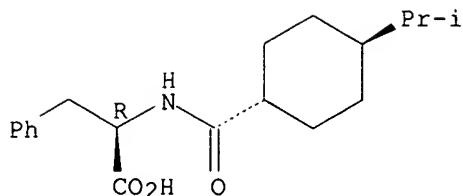
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001026639	A2	20010419	WO 2000-EP9816	20001006 <--
WO 2001026639	A3	20020110		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1218015	A2	20020703	EP 2000-972695	20001006 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
PRAI US 1999-415307	A	19991008 <--		
US 1999-415308	A	19991008 <--		

WO 2000-EP9816 W 20001006 &lt;--

## CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001026639	ICM	A61K0031-00
	IPCI	A61K0031-00 [ICM, 7]
	IPCR	A61K0031-445 [I, A]; A61K0031-445 [I, C*]; A61K0045-00 [I, C*]; A61K0045-06 [I, A]
EP 1218015	ECLA	A61K031/445+M; A61K031/70J+M; A61K045/06+M
	IPCI	A61K0031-70 [ICM, 6]; A61K0031-445 [ICS, 6]; A61K0031-195 [ICS, 6]; A61K0031-185 [ICS, 6, C*]; A61P0003-00 [ICS, 6]
	IPCR	A61K0031-445 [I, A]; A61K0031-445 [I, C*]; A61K0045-00 [I, C*]; A61K0045-06 [I, A]
AB	The invention relates to a combination which comprises nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose for simultaneous, sep. or sequential use, in particular in the treatment of diseases, especially metabolic disorders; to a method of prevention, delay of progression or treatment of metabolic disorders, more especially diabetes, or a disease or condition associated with diabetes, and to a method of improving the bodily appearance of a warm-blooded animal.	
ST	nateglinide antidiabetic antiobesity	
IT	Drug delivery systems (carriers; treating metabolic disorders with nateglinide)	
IT	Body weight (loss; treating metabolic disorders with nateglinide)	
IT	Crystal morphology (of nateglinide; treating metabolic disorders with nateglinide)	
IT	Antidiabetic agents Antiobesity agents (treating metabolic disorders with nateglinide)	
IT	Sulfonylureas RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (treating metabolic disorders with nateglinide)	
IT	50-99-7, Glucose, biological studies RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (metabolism of; treating metabolic disorders with nateglinide)	
IT	103-82-2D, Phenylacetic acid, derivs. 657-24-9, Metformin 2295-31-0D, Thiazolidinedione, derivs. 9004-10-8, Insulin, biological studies 56180-94-0, Acarbose 105816-04-4, Nateglinide 135062-02-1, Repaglinide RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (treating metabolic disorders with nateglinide)	
IT	105816-04-4, Nateglinide RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (treating metabolic disorders with nateglinide)	
RN	105816-04-4 HCAPLUS	
CN	D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)	

Absolute stereochemistry. Rotation (-).



L61 ANSWER 25 OF 26 HCAPLUS COPYRIGHT 2006 ACS on STN  
 AN 1995:964992 HCAPLUS  
 DN 124:155974  
 ED Entered STN: 06 Dec 1995  
 TI Crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine and methods for preparing them.  
 IN Sumikawa, Michito; Koguchi, Yoshihito; Ohgane, Takao; Irie, Yasuo; Takahashi, Satoji  
 PA Ajinomoto Co., Inc., Japan  
 SO U.S., 12 pp. Cont.-in-part of U.S. Ser. No. 166,144.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 IC ICM C07C0229-00  
 INCL 562450000  
 CC 63-5 (Pharmaceuticals)  
 Section cross-reference(s): 75

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5463116	A	19951031	US 1994-190460	19940202 <--
	US 5488150	A	19960130	US 1993-166144	19931214 <--
	CA 2114678	AA	19950802	CA 1994-2114678	19940201 <--
	CA 2114678	C	19990427		
PRAI	JP 1991-189696	A	19910730	<--	
	JP 1991-199453	A	19910808	<--	
	US 1992-921224	B1	19920729	<--	
	US 1993-166144	A2	19931214	<--	

CLASS

	PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
	US 5463116	ICM	C07C0229-00
		INCL	562450000
		IPCI	C07C0229-00 [ICM, 6]
		IPCR	C07C0231-00 [I, C*]; C07C0231-22 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
		NCL	562/450.000; 562/444.000; 562/445.000
		ECLA	C07C231/22; C07C233/63
	US 5488150	IPCI	C07C0239-00 [ICM, 6]
		IPCR	C07C0231-00 [I, C*]; C07C0231-22 [I, A]; C07C0233-00 [I, C*]; C07C0233-63 [I, A]
		NCL	562/450.000
		ECLA	C07C231/22; C07C233/63
	CA 2114678	IPCI	C07C0233-63 [ICM, 6]; C07C0233-00 [ICM, 6, C*]; A61K0031-195 [ICS, 6]; A61K0031-185 [ICS, 6, C*]
		ECLA	C07C231/22; C07C233/63

AB Stable crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine for pharmaceutical formulation may be produced by treating this compound with a solvent at a temperature of at least 10° and forming crystals in the solvent at a temperature of at least 10°. For

example, **crystals** may be formed by **crystallization** out of solution, or may be formed from solid particles of the compound suspended in a solvent. **Crystals** formed in this way have different m.p., IR spectrum and X-ray diffraction patterns from previously known forms of the compound and have enhanced processability, e.g., stability to grinding.

ST isopropylcyclohexylcarbonyl phenylalanine **crystn** grinding

IT **Crystallization**

Solvent effect

(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

IT Size reduction

(grinding, **crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-64-1, Acetone, uses 75-05-8, Acetonitrile, uses 7732-18-5, Water, uses

RL: NUU (Other use, unclassified); USES (Uses)

(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

IT 105816-04-4

RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

IT 173653-89-9

RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

IT 105816-04-4

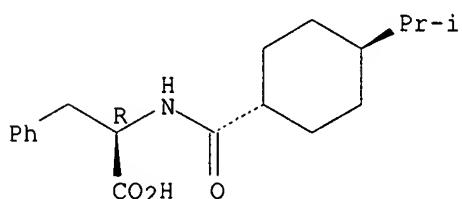
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

RN 105816-04-4 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 173653-89-9

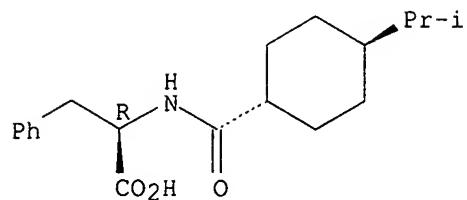
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)

RN 173653-89-9 HCPLUS

CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, hydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● x H<sub>2</sub>O

L61 ANSWER 26 OF 26 HCPLUS COPYRIGHT 2006 ACS on STN  
 AN 1993:261002 HCPLUS  
 DN 118:261002  
 ED Entered STN: 26 Jun 1993  
 TI Stable crystals of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine  
 IN Sumikawa, Michito; Koguchi, Yoshihito; Ohgane, Takao; Irie, Yasuo; Takahashi, Satoji  
 PA Ajinomoto Co., Inc., Japan  
 SO Eur. Pat. Appl., 14 pp.  
 CODEN: EPXXDW  
 DT Patent  
 LA English  
 IC ICM C07C0233-63  
 ICS A61K0031-195  
 CC 63-5 (Pharmaceuticals)  
 FAN.CNT 2

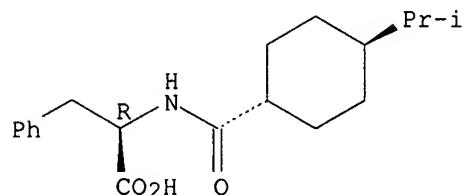
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PI	EP 526171	A2	19930203	EP 1992-306895	19920729 <--
	EP 526171	A3	19930505		
	EP 526171	B1	19970305		
	R: AT, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
	JP 05208943	A2	19930820	JP 1992-202686	19920729 <--
	JP 2508949	B2	19960619		
	AT 149483	E	19970315	AT 1992-306895	19920729 <--
	ES 2100291	T3	19970616	ES 1992-306895	19920729 <--
	CA 2114678	AA	19950802	CA 1994-2114678	19940201 <--
	CA 2114678	C	19990427		
PRAI	JP 1991-189696	A	19910730	<--	
	JP 1991-199453	A	19910808	<--	

CLASS

	PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
EP 526171	ICM	C07C0233-63	
	ICS	A61K0031-195	
	IPCI	C07C0233-63 [ICM,5]; C07C0233-00 [ICM,5,C*]; A61K0031-195 [ICS,5]; A61K0031-185 [ICS,5,C*]	
	IPCR	C07C0231-00 [I,C*]; C07C0231-22 [I,A]; C07C0233-00 [I,C*]; C07C0233-63 [I,A]	
	ECLA	C07C231/22; C07C233/63	
JP 05208943	IPCI	C07C0233-63 [ICM,5]; C07C0233-00 [ICM,5,C*];	

AT 149483      IPCI      C07C0231-24 [ICS,5]; C07C0231-00 [ICS,5,C\*];  
                   C07C0233-63 [ICM,6]; C07C0233-00 [ICM,6,C\*];  
                   A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C\*];  
                   C07C0231-22 [ICS,6]; C07C0231-00 [ICS,6,C\*];  
                   ES 2100291      IPCI      C07C0233-63 [ICM,6]; C07C0233-00 [ICM,6,C\*];  
                   A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C\*];  
                   C07C0231-22 [ICS,6]; C07C0231-00 [ICS,6,C\*];  
                   IPCR      C07C0231-00 [I,C\*]; C07C0231-22 [I,A]; C07C0233-00  
                   [I,C\*]; C07C0233-63 [I,A]  
                   CA 2114678      IPCI      C07C0233-63 [ICM,6]; C07C0233-00 [ICM,6,C\*];  
                   A61K0031-195 [ICS,6]; A61K0031-185 [ICS,6,C\*];  
                   IPCR      C07C0231-00 [I,C\*]; C07C0231-22 [I,A]; C07C0233-00  
                   [I,C\*]; C07C0233-63 [I,A]  
                   ECLA      C07C231/22; C07C233/63  
                   AB      Stable H-type **crystals** of N-(trans-4-  
                   isopropylcyclohexylcarbonyl)-D-phenylalanine (I) are obtained by treating  
                   I with a solvent, at >10°. A solution of 5 g I in 20 mL acetone was  
                   added to a stirred mixture of 40 mL acetone and 60 mL water, at 25°  
                   to precipitate H-type **crystals**. The **crystals** have different  
                   m.p., IR spectrum and x-ray diffraction patterns from known forms of I and  
                   are not converted to other forms when ground.  
                   ST      phenylalanine deriv drug stable **crystal**  
                   IT      105816-04-4P  
                   RL: PREP (Preparation)  
                   (crystals, stable, preparation of)  
                   IT      105816-04-4P  
                   RL: PREP (Preparation)  
                   (crystals, stable, preparation of)  
                   RN      105816-04-4 HCPLUS  
                   CN      D-Phenylalanine, N-[{trans-4-(1-methylethyl)cyclohexyl}carbonyl]- (9CI)  
                   (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



=> => d his

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   SET COST OFF

FILE 'REGISTRY' ENTERED AT 09:46:31 ON 14 JUN 2006  
   E NATEGLINIDE/CN

L1      1 S E3  
           E C19H27NO3/MF  
           L2      175 S E3 AND (46.150.18 AND 46.150.1)/RID AND 2/NR  
           L3      11 S L2 AND PHENYLALANINE  
           L4      7 S L3 AND METHYLETHYL  
           L5      6 S L4 NOT 14C  
           L6      2 S L5 AND NATEGLINIDE  
           L7      6 S L1,L5,L6

L8 1 S NATEGLINIDE NOT L7  
 SEL RN L7  
 L9 29 S E1-E6/CRN  
 L10 29 S L9 NOT MXS/CI  
 L11 6 S L10 NOT COMPD  
 L12 13 S L7,L8,L11  
 L13 23 S L9 NOT L12

FILE 'HCAPLUS' ENTERED AT 09:49:40 ON 14 JUN 2006

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 L15 4 S US20040181089/PN OR (US2003-622905# OR WO2004-US00839 OR US20  
 E YAHALOMI/AU  
 L16 3 S E7  
 E SHAPIRO/AU  
 L17 1 S E3  
 E SHAPIRO E/AU  
 L18 347 S E3-E20,E53-E57  
 E DOLITZKY/AU  
 L19 53 S E4,E5,E1  
 E DOLITZKI/AU  
 E GOZLAN/AU  
 L20 6 S E27-E29  
 E GOME/AU  
 L21 7 S E4,E5  
 E RONIT/AU  
 E SHAPIOR/AU  
 L22 1 S E4  
 E EVGENY/AU  
 E BEN ZION/AU  
 E BENZION/AU  
 E YIGAEL/AU  
 E BOAZ/AU  
 E TEVA/PA,CS  
 L23 393 S E3-E117  
 L24 5 S L14 AND L15-L23  
 L25 5 S NATEGLINID? AND L15-L23  
 L26 5 S L24,L25  
 L27 5 S L15,L26  
 E CRYSTAL/CT  
 E E62+ALL  
 L28 7068 S E1  
 E E2+ALL  
 L29 18069 S E2+OLD  
 E E14+ALL  
 L30 8940 S E2+OLD, NT  
 E CRYSTAL FORM/CT  
 E E105+ALL  
 L31 395901 S E1,E2  
 L32 28536 S E37,E39  
 L33 33798 S E105,E106  
 E E123+ALL  
 L34 53181 S E5  
 L35 37071 S E8-E15  
 E E23+ALL  
 L36 124126 S E4+NT  
 E E26+ALL  
 L37 4013 S E31  
 E CRYST/CT,CW  
 L38 648859 S E16  
 E CRYSTALL/CT,CW

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L40      107845 S E67,E68,E74,E75
          E CRYSTAL/CT,CW
L41      30 S L14 AND L28-L40
L42      21 S L41 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L43      23 S L27,L42
L44      34 S L14(L) PREP+NT/RL
L45      10 S L43 AND L44
L46      11 S L27,L45
L47      11 S L46 AND L14-L44
L48      12 S L43 NOT L47
L49      23 S L47,L48
L50      41 S L14(L) PROC+NT/RL
L51      56 S L44,L50 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L52      41 S L51 NOT L49
L53      3 S L52 AND ?CRYSTAL?
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L55      26 S L54 AND L14-L54
L56      25 S L55 AND ?CRYSTAL?
L57      15 S L55 AND CRYSTAL?/SC,SX
L58      14 S L14 AND CRYSTAL?/SC,SX AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L59      26 S L55-L58
L60      1 S L14 AND FORM U
L61      26 S L59,L60

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FILE 'HCAPLUS' ENTERED AT 10:10:23 ON 14 JUN 2006

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FILE 'REGISTRY' ENTERED AT 10:30:54 ON 14 JUN 2006  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
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Property values tagged with IC are from the ZIC/VINITI data file  
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STRUCTURE FILE UPDATES: 13 JUN 2006 HIGHEST RN 887650-39-7  
DICTIONARY FILE UPDATES: 13 JUN 2006 HIGHEST RN 887650-39-7

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

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*****
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,      *
* effective March 20, 2005. A new display format, IDERL, is now        *
* available and contains the CA role and document type information.  *
*****
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Structure search iteration limits have been increased. See HELP SLIMITS  
for details.

REGISTRY includes numerically searchable data for experimental and  
predicted properties as well as tags indicating availability of

experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

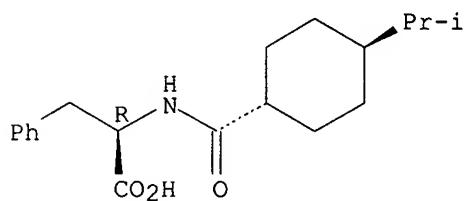
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 RN 651353-54-7 REGISTRY  
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 with heptane (9CI) (CA INDEX NAME)  
 FS STEREOSEARCH  
 MF C19 H27 N O3 . x C7 H16  
 SR CA  
 LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4  
 CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



From applicants'  
 pub w/  
 "Form U"

CM 2

CRN 142-82-5  
 CMF C7 H16

Me-(CH<sub>2</sub>)<sub>5</sub>-Me

1 REFERENCES IN FILE CA (1907 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

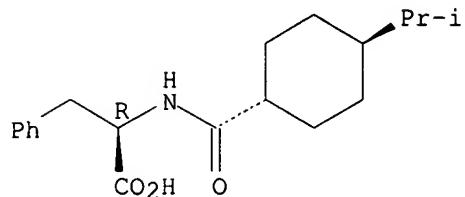
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L7 ANSWER 2 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN  
 RN 651353-53-6 REGISTRY  
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 with trichloromethane (9CI) (CA INDEX NAME)  
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 MF C19 H27 N O3 . x C H Cl3  
 SR CA  
 LC STN Files: CA, CAPLUS

CM 1

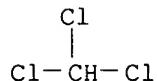
CRN 105816-04-4  
 CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 67-66-3  
 CMF C H Cl3



1 REFERENCES IN FILE CA (1907 TO DATE)  
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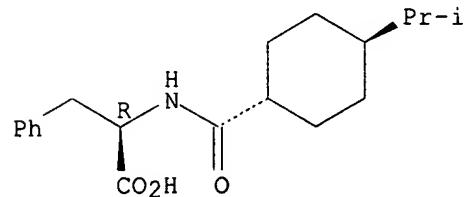
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 RN 651353-52-5 REGISTRY  
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 with 1,2-dichloroethane (9CI) (CA INDEX NAME)  
 FS STEREOSEARCH  
 MF C19 H27 N O3 . x C2 H4 Cl2  
 SR CA  
 LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4  
 CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 107-06-2  
 CMF C2 H4 Cl2

Cl-CH<sub>2</sub>-CH<sub>2</sub>-Cl

1 REFERENCES IN FILE CA (1907 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

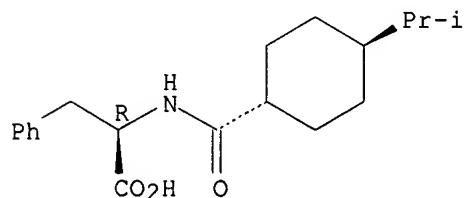
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L7 ANSWER 4 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN  
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 with tetrachloromethane (9CI) (CA INDEX NAME)  
 FS STEREOSEARCH  
 MF C19 H27 N O3 . x C Cl4  
 SR CA  
 LC STN Files: CA, CAPLUS

CM 1

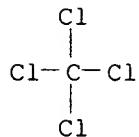
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 CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 56-23-5  
 CMF C Cl4



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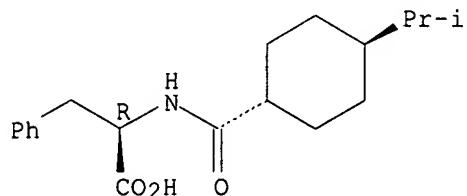
L7 ANSWER 5 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN  
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 ED Entered STN: 18 Feb 2004

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with dimethylbenzene (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C19 H27 N O3 . x C8 H10  
SR CA  
LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4  
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 1330-20-7  
CMF C8 H10  
CCI IDS



2 ( D1-Me )

1 REFERENCES IN FILE CA (1907 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

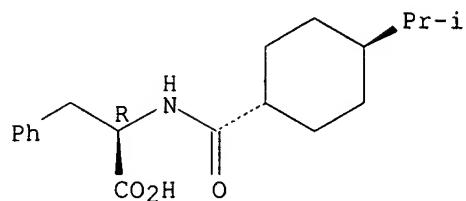
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with 1,2-dimethoxyethane (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C19 H27 N O3 . x C4 H10 O2  
SR CA  
LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4  
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 110-71-4  
CMF C4 H10 O2

MeO—CH<sub>2</sub>—CH<sub>2</sub>—OMe

1 REFERENCES IN FILE CA (1907 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

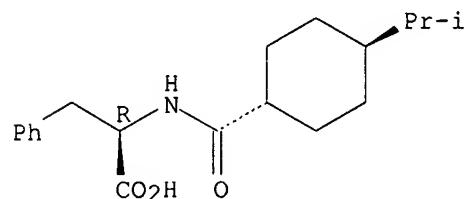
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ED Entered STN: 18 Feb 2004  
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with N,N-dimethylformamide (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C19 H27 N O3 . x C3 H7 N O  
SR CA  
LC STN Files: CA, CAPLUS

CM 1

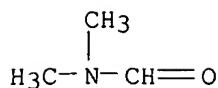
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CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 68-12-2  
CMF C3 H7 N O



1 REFERENCES IN FILE CA (1907 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

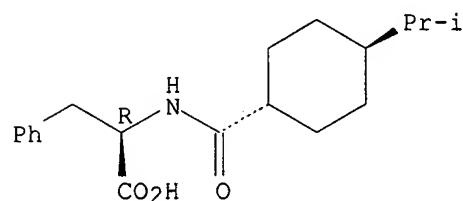
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 ED Entered STN: 18 Feb 2004  
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 with 1-methyl-2-pyrrolidinone (9CI) (CA INDEX NAME)  
 FS STEREOSEARCH  
 MF C19 H27 N O3 . x C5 H9 N O  
 SR CA  
 LC STN Files: CA, CAPLUS

CM 1

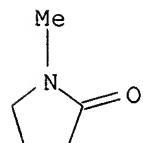
CRN 105816-04-4  
 CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 872-50-4  
 CMF C5 H9 N O



1 REFERENCES IN FILE CA (1907 TO DATE)  
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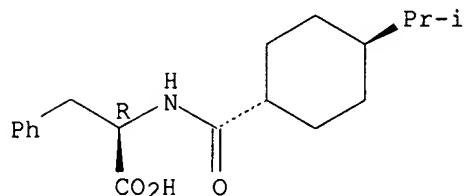
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 with N,N-dimethylacetamide (9CI) (CA INDEX NAME)

FS STEREOSEARCH  
 MF C19 H27 N O3 . x C4 H9 N O  
 SR CA  
 LC STN Files: CA, CAPLUS

CM 1

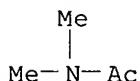
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 CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 127-19-5  
 CMF C4 H9 N O



1 REFERENCES IN FILE CA (1907 TO DATE)  
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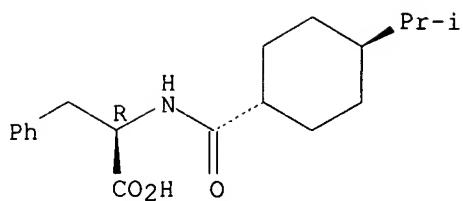
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L7 ANSWER 10 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN  
 RN 651353-45-6 REGISTRY  
 ED Entered STN: 18 Feb 2004  
 CN D-Phenylalanine, N-[(trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd.  
 with 1-propanol (9CI) (CA INDEX NAME)  
 FS STEREOSEARCH  
 MF C19 H27 N O3 . x C3 H8 O  
 SR CA  
 LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4  
 CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 71-23-8

CMF C3 H8 O

H<sub>3</sub>C—CH<sub>2</sub>—CH<sub>2</sub>—OH

1 REFERENCES IN FILE CA (1907 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:151932

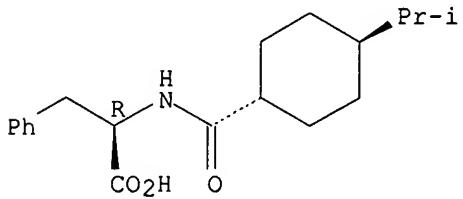
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 ED Entered STN: 18 Feb 2004  
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 with 1-butanol (9CI) (CA INDEX NAME)  
 FS STEREOSEARCH  
 MF C19 H27 N O3 . x C4 H10 O  
 SR CA  
 LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4

CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 71-36-3

CMF C4 H10 O

H<sub>3</sub>C—CH<sub>2</sub>—CH<sub>2</sub>—CH<sub>2</sub>—OH

1 REFERENCES IN FILE CA (1907 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

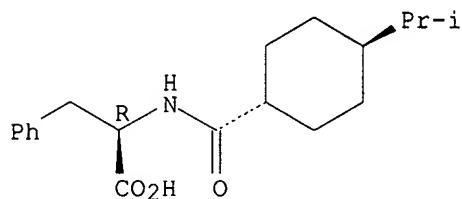
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 RN 651353-43-4 REGISTRY  
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 with ethanol (9CI) (CA INDEX NAME)  
 FS STEREOSEARCH  
 MF C19 H27 N O3 . x C2 H6 O  
 SR CA  
 LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4  
 CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 64-17-5  
 CMF C2 H6 O

H3C-CH2-OH

1 REFERENCES IN FILE CA (1907 TO DATE)  
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:151932

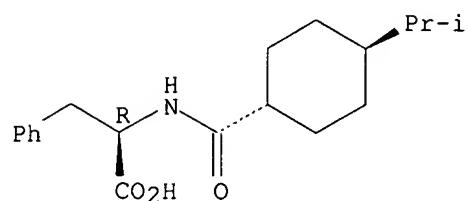
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 ED Entered STN: 18 Feb 2004  
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 with methanol (9CI) (CA INDEX NAME)  
 FS STEREOSEARCH  
 MF C19 H27 N O3 . x C H4 O  
 SR CA  
 LC STN Files: CA, CAPLUS

CM 1

CRN 105816-04-4

CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 67-56-1  
CMF C H4 O

H3C-OH

1 REFERENCES IN FILE CA (1907 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:151932

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